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GENE THERAPY ADVISORY COMMITTEE

EIGHTH ANNUAL REPORT

January 2001 – December 2001

Health Departments of the United Kingdom
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FOREWORD

Since 1993, GTAC has attempted to engage the wider public, with the aim of both promoting an understanding of gene therapy and providing a platfom for dialogue and feedback. In 2001, GTAC hosted a public workshop on *Gene Therapy for Inherited Disorders*. As well as presentations of highly encouraging results from international gene therapy trials for X-linked Severe Combined Immunodeficiency (X-SCID) and Haemophilia, there were a number of round-table discussions on the future of gene therapy for single-gene disorders. Over the past two years, GTAC has seen a significant expansion in the number of submitted gene therapy protocols. However, in the continuing trend towards the potential use of gene therapy in the treatment of cancer, about 75% of gene therapy protocols in 2001 involved cancer patients. The remainder focussed on research into management of diseases of the vascular system and into controlling viral infection. Disappointingly, no protocols involving single gene disorders were reviewed by the committee this year. The apparent shift in gene therapy research away from inherited disorders and towards management of chronic illness perhaps reflects the current limitations of the tools of the trade. The present generation of gene therapy vectors offer quite localised delivery of therapeutic products and typically yield only short-lived gene expression. It is now clear that successful gene therapy is much more complex and involves many more critical steps than initially realized. Despite this, it is encouraging to see major advances from academia towards potential treatments for several of the single-gene disorders, such as X-SCID and chronic granulomatous disease. In addition, the development of new tools aimed at ensuring more wide-spread and longer-term gene expression in patients are being actively pursued in the laboratory. Given the smaller patient populations, commercial interest in developing treatment for single-gene disorders is markedly less than for the cancers, coronary artery disease or infectious disease. One of the conclusions from our 2001 workshop was that research into single-gene disorders may require special allocations of public funding in order to fulfil its potential promise.

Professor Norman C Nevin
Chairman of GTAC

SECTION 1: PROTOCOLS REVIEWED BY GTAC IN 2001

GTAC reviewed nineteen proposals and received two notifications to conduct gene therapy research in 2001. Of these, thirteen were reviewed in full committee, while five were assessed by expedited review. Seventeen of the studies were approved, while resubmission of applications were invited in two cases. Neither of the notifications received objection.

MELANOMA

Malignant melanoma is an increasingly common form of skin cancer. In the United States, for example, the number of new cases of melanoma has more than doubled in the last 20 years. It accounts for approximately 1500 cancer deaths a year in this country. It occurs most commonly in the trunk, head, neck or limbs when melanocytes, the pigment producing cells in the epidermal layer, divide and proliferate abnormally. Although surgery can often successfully treat this type of tumour, if the cancer has spread or if it recurs, successful treatment is unlikely.

Antigens are molecules of the cell that the immune system uses for recognition. The complement of antigens a cell possesses determines whether it is seen as 'self' or 'foreign.' Whilst tumour cells show alterations in their profile of antigens, the immune system may fail to recognise them as foreign. Melanoma cells have a number of antigens not normally seen on other cells. One notion for a potential treatment of cancer posits that the immune system could be 'educated' to detect such tumour cells using these antigens.

The immune system has a variety of specialised cells, such as Antigen Presenting Cells (APCs) or Dendritic Cells (DCs), whose function is to process antigens and present them for recognition by the immune system. Any particular antigen may have a variety of contours, surfaces or stretches of amino acids that the immune system uses for recognition. These are known as epitopes. Once APCs encounter foreign molecules, they internalise them, break them down and export them out to their cell surface. The APCs display the antigens to T-cells (or Cytotoxic T-Lymphocytes or CTLs), which produce the appropriate immune attack. These T-cells then begin to multiply and act against the cell with the foreign antigen.

GTAC049: A phase I/II study of immunotherapy for patients with metastatic melanoma using dendritic cells transfected with a plasmid encoding two melanoma antigens. University of Birmingham.

In this proposal, the investigators wish to take DC precursors from the blood of patients with melanoma and then generate and harvest DCs. These DCs will then be transformed *ex vivo* with a plasmid encoding two melanoma antigens, known as MART-1 and gp-100, using a novel non-viral delivery system, CL22. This is based on a peptide from the influenza virus nucleoprotein, which is complexed with the plasmid for transfection purposes. The DCs will be injected into patients, close to lymph nodes and their immune system responses will be monitored. The proposal was reviewed in full committee in February 2001 where it was awarded conditional approval. Final approval was granted in November 2001.

GTAC065: A phase I trial of polyMEL, a polyepitope DNA vaccine in the treatment of metastatic melanoma. St James's University Hospital, Leeds.

In this study, the proposers hope that vaccination with a DNA plasmid will stimulate an immune response to proteins found in melamona cells and, as a consequence, induce a reaction against the cancer cells themselves. The DNA plasmid vaccine carries eight portions of proteins (or epitopes) which the immune system can recognise. The chosen epitopes are derived from proteins which are commonly expressed on melanoma cells. The proposers will give melanoma patients intramuscular injections of this DNA and examine any potential immune responses. This proposal was reviewed in full committee in December 2001 and awarded conditional approval. Final approval was granted in January 2002.

HEAD AND NECK CANCER

Head and neck cancers make up about 4% of all new cancers in the UK. Risk factors for head and neck cancer include tobacco smoking or tobacco chewing and alcohol consumption. These cancers are more common in men but incidence has fallen over recent years, perhaps due to better oral hygiene and less tobacco and spirit consumption. If detected early, irradiation and surgery can be effective treatment. However, at advanced stages of the disease radical procedures involving mutilating surgery, irradiation or chemotherapy produce poor results. Recurrence of these tumours reduces the patient's quality of life as well as reducing their chances of survival.

GTAC050: A phase II trial of preoperative intratumoral injection with HSV1716 in patients with resectable squamous cell tumours of the head and neck. University of Glasgow.

Herpes Simplex Virus (HSV) causes cold sores, genital herpes and, in extreme cases encephalitis. The HSV1716 virus has been derived from HSV. However, HSV1716 is a mutant version of the normal virus which can replicate in tumour cells but which has an impaired ability to replicate in normal cells. In this study, primarily designed to assess the safety of the virus, up to fifteen patients will receive an injection of the HSV1716 virus in tumours of the head and neck. Viral replication and spread within tumours will then be examined. This study was reviewed by GTAC in March 2001 and awarded approval in May 2001.

CORONARY ARTERY DISEASE

Heart muscle requires a constant supply of oxygen to maintain normal function. This is provided by the blood through a network of vessels via the coronary arteries. Coronary artery disease (CAD) is the end result of "hardening of the arteries" (atherosclerosis), where fatty deposits build up on the sides of vessels and interfere with normal blood flow. When blood flow is restricted by such plaque formation (stenosis), the heart muscle may become deprived of oxygen (ischaemia). This can result in muscle tissue damage and is typically experienced as chest pain (angina). In severe cases this may lead to heart attack (myocardial infarction).

Depending on the location and severity of the problem, some CAD can be treated through a combination of drug therapy and lifestyle changes. When severe, it may be possible to bypass the blockage by taking a vein from the leg (or the mammary or radial artery) and connecting

it above and below the blockage. This process is known as coronary artery bypass grafting (CABG). This allows blood and oxygen to reach areas of the heart muscle that had been impaired by the blocked flow. For some patients there are areas of the heart that CABG cannot help, for example where arteries are too small to be amenable to bypass grafting or in areas of very diffuse disease. A second intervention, known as balloon angioplasty (percutaneous transluminal coronary angioplasty; PTCA), involves the use of a catheter to guide a balloon-tipped tube to the site of the arterial blockage. When the balloon is inflated the arterial deposit is compacted, thus widening the artery and increasing the blood-flow.

As a result of CAD or heart attack, new blood vessels can form in an attempt to increase the blood (and consequently oxygen) supply to the heart. A novel therapeutic approach to CAD involves trying to stimulate the body to produce new blood vessels to the heart muscle to meet its oxygen requirements. This process is referred to as therapeutic angiogenesis.

GTAC051: A European and Canadian multicentre, randomised, double-blind, placebo controlled, dose-response study to evaluate the efficacy and safety of Ad5FGF-4 in patients with stable angina. Papworth Hospital, Cambridge.

This is a multicentre study with up to 350 patients to be enrolled. It is a phase I, double-blind, placebo controlled gene therapy trial in patients with stable angina, who are currently not suitable candidates for PTCA or CABG surgical intervention. Following angiography, which is to be performed as part of the patients' routine diagnostic management, subjects (confirmed as suitable for trial participation by an independent consultant) will be injected into the coronary artery with an adenoviral vector (Ad5FGF-4) engineered to express the protein, Fibroblast Growth Factor-4 (FGF-4). This molecule has been shown to stimulate blood vessel formation in pre-clinical studies. The committee assessed an original version of this protocol and awarded conditional approval to a revised version in May 2001. Final approval was granted in September 2001.

GTAC067: Percutaneous intramyocardial gene therapy against myocardial ischaemia with phVEGF-A165SR – A double-blind placebo controlled study. Wythenshaw Hospital, Manchester.

This study involves the use of a DNA plasmid encoding a growth factor known as VEGF, vascular endothelial growth factor. The VEGF molecule has been shown to stimulate blood vessel formation in animal models. Here, it is proposed to inject the VEGF plasmid into the heart of patients with Coronary Artery Disease. The proposal is currently under review.

HEPATITIS B VIRUS

The Hepatitis B virus (HBV) is one of the most common human pathogens, with an estimated 280-350 million carriers globally. This accounts for about 5% of the world's population. The virus is primarily spread by intimate contact with bodily fluids, such as blood, semen, breast milk or even saliva. Once infected the majority of people (around 90%) develop antibodies and recover spontaneously.

The remainder become chronically infected and whilst they may show no signs or symptoms of infection, the virus remains in the blood and can infect others. In 20-30% of chronic HBV carriers, the virus continues its attack on the liver leading to cirrhosis and possibly liver cancer.

Whilst chronic HBV infection can be treated with antiviral drugs such as lamivudine, there is currently no cure. Although a number of somewhat effective preventative vaccines (based on recombinant viral proteins) have been developed, no therapeutic ones are currently available.

Trials involving similar vectors have previously been approved by the GTAC for: (1) studies of HPV vaccines in cervical, vulval and ano-genital intraepithelial neoplasia III, (2) Mel3 "prime-boost" studies in melanoma, and (3) studies involving MUC-I and IL2 in breast cancer. Gene therapy in healthy subjects has previously been approved by GTAC for studies involving DNA idiotypic vaccination.

GTAC052: A phase I study to evaluate the safety, tolerability and immunogenicity of two administrations of either plasmid DNA (pSG2.HBs) versus placebo or modified Vaccinia virus Ankara (MVA.HBs) versus placebo, followed by two boost adminsitrations of MVA.HBs expressing Hepatitis B surface antigen, in healthy male volunteers. TNO BIBRA, Surrey.

This study is a phase I trial to evaluate safety, tolerability and immunogenicity of the DNA/MVA treatment regime. Eighteen healthy male volunteers will be injected with naked DNA plasmid and modified Ankara vaccinia virus (MVA). The Ankara vaccinia virus has previously been used in smallpox eradication programmes. Both the DNA and MVA vectors are engineered to express HBV surface proteins (antigens). The use of both plasmid and viral vectors is referred to as the "prime-boost" strategy. It would appear that the immune system produces a more robust response when two different systems expressing the same antigen are used in vaccinations. The presence of the HBV proteins should cause an immune system response to HBV antigens in the healthy subjects, with the ultimate hope of producing immunity to HBV. The protocol was reviewed and awarded conditional approval in May 2001 and awarded final approval in August 2001.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

Human Immunodeficiency Virus (HIV) is the agent responsible for Acquired ImmunoDeficiency Syndrome (AIDS). Once infected, the virus replicates and spreads through the immune system. The virus depletes cells of the immune system, called CD4 T-lymphocytes which are responsible for fighting infections. Such loss of immune system activity exposes those infected to opportunistic infections and tumour proliferation.

By 2000, it has been estimated that 50 million people worldwide were infected with HIV. It is estimated that 16,000 people throughout the world are infected with HIV each day. Over 90% of these new infections occur in the developing world, especially in sub-Saharan Africa and Asia, where the vast majority of people have little or no access to effective medical treatment.

Although Highly-Active Antiretroviral Therapy (HAART) has been relatively successful in treating HIV infection, it is limited by toxicity, the development of resistant forms of virus and has significant side effects. There is, therefore, a need for additional and alternative treatment programmes. Despite innovative preventative efforts, safe and effective HIV prophylatic and therapeutic vaccines are needed to bring the HIV/AIDS epidemic under control.

GTAC053: 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 antiretroviral therapy. MRC Human Immunology Unit, University of Oxford.

This proposal is part of a wider study involving a "prime-boost" strategy which uses modified vaccinia virus (MVA) and plasmid DNA to develop both therapeutic and prophylactic vaccines against HIV infection. Plasmid DNA will be injected into HIV-seropositive patients so that safety and immunogenicity can be evaluated before further therapeutic studies. The DNA construct is designed to express several HIV-specific proteins (and portions of proteins known as *epitopes*) designed to raise an immune response against the virus. The plasmid has already been shown to induce immune responses in pre-clinical studies and is currently being employed in a phase I clinical trial as a prophylactic vaccine in healthy volunteers at Oxford. The study was reviewed and awarded conditional approval in May 2001. Final approval was granted in May 2002.

PERIPHERAL ARTERIAL OCCLUSIVE DISEASE

Peripheral Arterial Occlusive Disease (PAOD) occurs when atherosclerosis blocks blood flow through the large arteries of the legs. This results in ischaemia or loss of oxygen supply because of the restricted blood circulation. This condition is typically highly disabling and painful for those afflicted, leading to difficulty in walking, tissue damage (the appearance of ulcers), necrosis (gangrene) and ultimately the requirement for amputation of the affected limb. Risk factors associated with the disease include smoking, diabetes, distal arterial disease, high blood pressure, and hyperlipidemia. The disease afflicts up to 500 per million each year in the developed world.

PAOD patients have few treatment options, especially when attempts such as balloon angioplasty have failed to alleviate the condition. Typically, one of the few remaining options is amputation.

GTAC054: A phase II, randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of NVFGF1 in patients with severe peripheral artery occlusive disease. St. George's Hospital, London.

For this study, it is proposed to use a plasmid vector to express a molecule, Fibroblast Growth Factor-1 (FGF-1), which may stimulate new vessel growth in the affected legs. This approach is known as therapeutic angiogenesis. One hundred and twenty-two patients will be enrolled in this study. A DNA plasmid, designated NVFGF1, will be injected into calf and thigh muscle tissue of the affected legs of patients. Patients will be assessed for changes in pain levels, ulcer severity and amputation frequency. The proposal was considered in full committee and awarded conditional approval in July 2001. Final approval was granted in November 2001.

PROSTATE CANCER

The prostate gland is an organ of the male reproductive system located between the pubic bone and the rectum. It produces clear fluid to help protect sperm as it passes through the urethra. Prostate cancer tends to occur in older men, with 95% of cases occurring in men over the age of 60. It is the third most common cause of cancer death in the UK with 12,000 new cases each year. Unchecked division of cancerous cells in the prostate leads to enlargement of the organ. If detected early, surgery and/or radiotherapy can be highly effective treatments. However in an advanced state, when spread beyond the prostate to other sites, such as the pelvic bone, treatment options are very limited.

GTAC055: Gene directed enzyme prodrug therapy for the treatment of prostate cancer (phase I intratumoral). University of Birmingham.

In this study a replication-deficient adenovirus will be injected into the prostate tumours of 15 to 30 patients. The virus carries a gene that codes for a "pro-drug activating enzyme" which converts an inert drug (pro-drug) into a toxic substance capable of killing cells. After intra-tumoural injection the virus should infect tumour cells. Once inside the cells, the virus cannot further reproduce but will produce the pro-drug activating enzyme. When the pro-drug is administered to patients, it should be converted to the toxic compound only in tumour cells.

This study was submitted for review in November 2000 and was granted approval in February 2001.

GTAC061: An upward titration study of transfection efficacy and safety of MetXia-OB83 in patients with adenocarcinoma of the prostate. The Christie Hospital, Manchester.

This study will involve twenty patients with recurrent prostate cancer. The study agent is a modified retrovirus that encodes a pro-drug activating enzyme. The virus will be injected under ultrasound imaging into the prostate tumour. Patients will then be given the pro-drug and effects on the tumour assessed.

This study was submitted for consideration by GTAC in April 2001 and awarded approval in September 2001.

INTRAEPITHELIAL NEOPLASIA

Human Papilloma Virus (HPV) infection is believed to be a significant risk factor associated with the long-term development of cervical, vulval or ano-genital cancers. Once a cell is infected, the virus integrates into the genome and over-expresses two proteins, E6 and E7. These are proteins that cause the infected tissue to "transform" into a pre-cancerous state, called neoplasia. HPV types 16 and 18 are most commonly associated with intraepithelial neoplasias. Eventually, persistent infection of this type of tissue can become cancerous and result in "full-blown" cervical, vulval or ano-genital cancer.

Antigens are molecules on the surface of cells that the immune system uses for recognition purposes. The variety of antigens that a cell possesses determines whether it is seen by the immune system as 'self' or 'foreign.' Cells infected with HPV may show alterations in their

profile of antigens. Specialised cells within the immune system, the Anitgen Presenting Cells (APCs), help T-cells to identify and mount an attack on abnormal cells. In this way, the immune system may recognise a transformed cell as 'foreign' and mount a response against the HPV-infected tissue.

GTAC056: A phase II, multicentre, double-blind, placebo-controlled, dose-finding study of ZYC101a in the treatment of high-grade squamous intraepithelial lesions of the uterine cervix. Hammersmith Hospital, London.

The aim of this DNA vaccine study is to allow the patients' immune systems to view HPV-infected cells as "foreign" and to stimulate an immune system rejection of those cells from the body. The proposers wish to use a plasmid encoding epitopes (portions of proteins effective at eliciting immune responses) of the E6 and E7 proteins from HPV16 and HPV18. The plasmid will be packaged into particles that are designed to be taken up by APCs in particular. If successful, the APCs will express the HPV antigens. This could induce T-cell-mediated immune responses directed against those cells infected with HPV, with possible alleviation of the HPV-associated neoplasia. The proposal was reviewed in full committee in July 2001 and conditional approval was awarded in November 2001.

GTAC059: TA-HPV recombinant vaccinia virus expressing the human papillomavirus 16 and 18 E6 and E7 proteins: Application to amend currently approved protocol to add a clinical trial involving a prime-boost strategy of TA-CIN administered in association with TA-HPV in high grade ano-genital intraepithelial neoplasia (AGIN) patients. University of Wales, Cardiff.

TA-HPV has been developed from Vaccinia virus, the live vaccine used extensively in smallpox eradication programmes. TA-HPV is a genetically modified vaccine which carries the E6 and E7 genes from HPV. By injecting this engineered virus into patients muscle, it is hoped that the patients' immune system will be stimulated to recognise HPV-infected cells (expressing E6 and E7 proteins) as "foreign" and mount an attack on them. In this way, HPV-infected cells of the ano-genitial region, with the potential to become cancerous, may be destroyed by the body's own defences. This proposal aims to build on experience gained in previous trials to use a combination of both TA-HPV and a protein-based vaccine against HPV called TA-CIN. GTAC reviewed this proposal in May 2001 and awarded approval in July 2001.

BREAST CANCER

Breast cancer remains a leading cause of death in England in women over 35 years of age. Whilst early diagnosis, surgery, radiotherapy and chemotherapy have improved patients' prospects, in the event of cancer spread or patient relapse, the prognosis can often be poor. Consequently, a variety of experimental approaches are being pursued in order to improve the prospects for these patients.

GTAC057: A phase I, multidose study to evaluate the safety of intramuscular injections of HER-2 DNA AutoVacTM (ME 103.1.1) in patients with metastatic breast cancer. Hammersmith Hospital, London.

HER-2, found on the surface of some cells, is a receptor which responds to signals from growth factors. In particularly aggressive forms of breast cancer, approximately 25% of cases,

the HER-2 receptor is found at higher levels. This leads to both a signal for uncontrolled growth and is typically indicative of a poor prognosis for such patients. Furthermore, HER-2-positve breast cancer can often be resistant to effective breast cancer treatments, such as tamoxifen and other chemotherapeutic agents. Targeting immune responses to the HER-2 receptor is one experimental approach to treatment of the disease. Recently a monoclonal antibody against HER-2 has been used in the treatment of HER-2-positive breast cancer.

The current study involves injection of a plasmid encoding the HER-2 receptor that has been "fused" to portions (epitopes) of the highly immunogenic tetanus toxin. The DNA should be taken up by cells in injected tissue, facilitating expression of the HER-2 modified protein. This could induce T-cells to attack HER-2-positive cancer cells. Given that plasmid DNA does not appear to persist long-term in the body, the proposers expect to obtain only transient expression of the fusion protein. This may be sufficient to induce immune responses to "highly HER-2"-positive cells. The study was reviewed and granted conditional approval in September 2001. Final approval was granted in October 2001.

GTAC058: The use of a cDNA vaccine encoding the human MUC-1 gene in the treatment of patients with advanced breast cancer – A phase I/II study. Guy's Hospital, London.

The goal of the present study is to vaccinate patients with the vector in the hope of stimulating an immune response that will recognise and destroy breast cancer cells. MUC-1 belongs to a family of proteins which are expressed on the surface of a wide variety of epithelia. The MUC-1 gene encodes a protein that is chemically-modified (glycosylated) by some of the cellular machinery and is known as a glycoprotein. The majority of the protein lies outside of the cell and is made up of a repeated structure. In 90% of breast cancers, MUC-1 protein levels are not only higher than in normal cells but also the protein is chemically modified. This means that in some cancers, such as breast cancer, MUC-1 may "look different" when compared to the protein found in healthy cells. Immune responses to MUC-1 products have been recorded in patients with advanced malignancy, including patients with breast and ovarian cancer.

This study proposes to use a plasmid vector carrying the gene for human MUC-1. This will be injected intramuscularly into the upper arm. It is hoped that this will allow cells of the patients' immune system to take up the plasmid encoding MUC-1. Expression of this protein in cells such as Antigen Presenting Cells (APCs) may influence T-cells to recognise those MUC-1 positive breast cancer cells as "foreign" and mount an attack on them.

This study was reviewed in full committee in July 2001 and granted conditional approval. Final approval was awarded in August 2001.

GTAC060: Study of transfection efficacy and safety of MetXia-OB83 in patients with cutaneous lesions of breast cancer or melanoma. The Churchill Hospital, Oxford.

This study will involve fourteen patients with advanced breast cancer or melanoma. The study agent is a replication-disabled retrovirus that encodes a "pro-drug activating enzyme." This enzyme converts a chemical (a pro-drug) into an active toxic drug, which is capable of killing cells. The first group of eight patients will be split into two different viral dosage groups. Virus will be injected into the tumour nodules of patients, who will also receive the

pro-drug. In theory, only in injected cells will the pro-drug be converted to the toxic drug. Patients tumours will be assessed for any effects from the viral injections and pro-drug administration. Following on from this, a further six patients will receive the pro-drug along with injections of optimal dose of virus (as determined by responses from the first group of patients). This proposal was submitted for consideration in April 2001 and awarded approval in September 2001.

GTAC062: First administration to man of an oncolytic Herpes virus vector containing a transgene for granulocyte macrophage colony stimulating factor (OncoVex^{GM-CSF}) – A study of its safety, biodistrubution and biological activity. Hammersmith Hospital, London.

A virus derived form Herpes Simplex Virus (HSV) will be used as a potential treatment of solid tumours. This vector, known as OncoVex, has been developed following initial reports of the safety and potential efficacy of other approaches using cancer cell killing (oncolytic) viruses.

The proposers wish to administer the study product to solid tumours on or just under the skin. The patient population includes those with breast cancer, head and neck cancer, melanoma, gastrointestinal and pancreatic cancers, which can spread to the skin. HSV results in death of infected cells which is likely to cause the release of proteins (or antigens) from these cells which can then be recognised by the immune system. Once stimulated, it is hoped that the immune system could mount an attack on the tumour tissue.

The study virus is deleted for two genes, known as ICP34.5 and ICP47. The virus also expresses Granulocyte Macrophage Colony Stimulating Factor (GM-CSF), which stimulates the growth and maturity of cells of the immune system, known as dendritic cells, which are responsible for recognising "foreign" antigens. This may induce systemic immune responses against infected cells because GM-CSF-stimulated dendritic cells can then take up these antigens and present them to the immune system. As with normal HSV, the study virus remains sensitive to anti-viral agents, such as acyclovir. This is because the HSV thymidine kinase gene is still present. Thus, any unforeseen problems associated with administration of OncoVex could be treated with this type of drug.

The study was considered in full committee in October 2001 and awarded conditional approval. Final approval was granted in November 2001.

GTAC068: A Phase I trial of polyHER2neu – a polyepitope DNA vaccine encoding HER-2 epitopes in the treatment of breast cancer. St James University Hospital, Leeds.

In particularly aggressive forms of breast cancer, approximately 25% of cases, the HER-2 receptor is found at higher levels. This high level is diagnostic of a poor prognosis and is indicative of uncontrolled growth. Furthermore, HER-2-positve breast cancer can often be resistant to effective breast cancer treatments, such as tamoxifen and other chemotherapeutic agents.

The investigators will use a DNA plasmid encoding portions of the HER-2 protein. By injecting a DNA plasmid into patients, it is hoped to stimulate cells of the immune system to recognise and kill breast cancer cells overexpressing HER-2. The DNA should be taken up by cells in injected muscle, facilitating expression of the HER-2 polyepitopes locally and within the immune system. This could induce T-cells to attack such HER-2-positive cancer cells. Given that plasmid DNA does not appear to persist long-term in the body, the proposers expect to obtain only transient expression of the gene product.

The study was reviewed in full committee in December 2001 and awarded conditional approval in January 2002.

COLORECTAL CANCER

Colorectal cancer is the second most common cause of cancer-related deaths in the UK. It accounts for 28,000 new cases and 19,000 deaths annually. Surgery offers the only form of curative treatment, if performed before there is tumour spread. The most common site for metastases is in the liver. In a small proportion of patients surgical removal of the liver tumour may be successful but the overall prognosis for the majority of patients with colorectal liver metastases remains poor.

One gene therapy approach to the treatment of such cancer involves the use of viruses that selectively replicate and kill tumour cells while being relatively harmless to normal cells. These conditionally replicating viruses are also referred to as *oncolytic viruses*.

GTAC063: 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. Hammersmith Hospital, London.

VTP-1 is an "oncolytic Adenovirus" that contains two deletions in its genome, known as E1A and E3B. The product is a virus that is capable of replicating in cells with defective cell division control (such as almost all cancer cell types), but which replicates extremely poorly in (and should therefore be relatively non-toxic to) non-dividing cells.

The proposers have published research demonstrating that the VTP-1 virus can replicate in a variety of tumour cell types and significantly reduce tumour activity in pre-clinical models.

This proposal was submitted for review in December 2001 but later withdrawn by the proposers. Re-submission of an application to GTAC was invited.

MESOTHELIOMA

The mesothelium is a protective lining for the internal organs of the body, such as the lungs. It is made up of two sheets of cells. One sheet closely wraps around the organs while the other forms a pouch around it. The mesothelium produces a fluid to lubricate both sheets as organs move during normal bodily activity, such as breathing. Mesothelioma (or cancer of the mesothelium) is a disease in which cells of the mesothelium divide without control or order. Once in a cancerous state, these cells can invade and damage nearby tissues and organs.

While rates of mesothelioma have increased in the past 20 years, it is a relatively rare form of cancer. Around 1,300 new cases are diagnosed in the UK each year. Exposure to asbestos is one of the major risk factors for development of mesothelioma. Although surgery, radiotherapy and chemotherapy are used to combat this disease, in general, their role is the relief of pain rather than in cure or treatment.

GTAC064: A phase I trial of replication-competent Herpes simplex virus (ICP 34.5 null mutant 1716) in patients with inoperable malignant pleural mesothelioma. University of Glasgow.

The investigators will administer a derivative, known as HSV1716, of *Herpes simplex* virus (the virus that causes cold sores) to patients with inoperable mesothelioma. HSV1716 contains a deletion in the ICP34.5 gene which effectively blocks its ability to replicate in non-dividing cells. However, HSV1716 can still efficiently replicate in and kill proliferating cells such as tumour cells. HSV1716 has been used safely in phase I studies in the treatment of melanoma, head and neck cancer and glioma. There is also some indication that it can be efficacious in the treatment of certain tumours.

This study was reviewed in full committee in December 2001 and awarded conditional approval in January 2002. Final approval was granted in February 2002.

SECTION 2: PROTOCOL NOTIFICATIONS TO GTAC

In 2000, GTAC revised its definition of gene therapy to ensure appropriate regulatory oversight of all clinical research involving the introduction of genetic material into human subjects. The revised definition now includes studies involving the use of DNA vaccination in healthy volunteers. Studies such as these are notified to GTAC and can proceed unless objection is raised.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

By 2000, it has been estimated that 50 million people worldwide were infected with HIV. It is estimated that 16,000 people throughout the world are infected with HIV each day. Over 90% of these new infections occur in the developing world, especially in sub-Saharan Africa and Asia, where the vast majority of people have little or no access to effective medical treatment. Although Highly-Active Antiretroviral Therapy (HAART) has been relatively successful in treating HIV infection, it is limited by toxicity, the development of resistant forms of virus and has significant side effects. There is, therefore, a need for additional and alternative treatment programmes. Despite innovative preventative efforts, safe and effective HIV prophylatic and therapeutic vaccines are needed to bring the HIV/AIDS epidemic under control.

NOTIFICATION ONE:

A single centre, open label, dose escalating phase I study to evaluate the safety and immunogenicity of a candidate HIV-1 clade A DNA vaccine delivered intramuscularly by a needle injection and a candidate HIV Clade A MVA vaccine delivered intradermally by a needle injection in healthy volunteers at low risk of HIV infection. University of Oxford.

This proposal is part of a wider study involving a "prime-boost" strategy which uses modified vaccinia virus (MVA) and plasmid DNA to develop prophylactic vaccines against HIV infection. The DNA and MVA constructs are designed to express several HIV-specific proteins (and portions of proteins known as *epitopes*) which may cause the immune system to raise a response against the virus. In this study, two groups of nine volunteers will receive two doses of the DNA plasmid via intramuscular injection, followed by two doses of the MVA vector via intradermal injection. Immune system responses to the HIV-specific epitopes will be examined in volunteers.

The study was notified to GTAC in May 2001. As no objections were raised, the notification was duly accepted by the committee.

MALARIA

Malaria causes the greatest number of childhood deaths in the world. The World Health Organisation estimates that there are annually 300-500 million cases of this infection, with over a million deaths. Infection occurs when a mosquito, infected with the malarial pathogen *Plasmodium falciparum*, bites an individual, allowing the pathogen to enter the blood system. After reproducing in the infected-person's liver, the pathogen travels to the red blood cells

where it multiplies, releasing toxins and bursting the cells. Symptoms may progress from flu-like fever to jaundice, to organ failure, coma and death. Once infected, malaria is extremely difficult to eradicate.

NOTIFICATION TWO:

Prime-boost immunisation strategies for prophylactic vaccination against Plasmodium falciparum malaria: safety and immunogenicity studies. University of Oxford.

In this study, the investigators aim to stimulate the immune system to respond to proteins of the malarial parasite using a genetic vaccination strategy. They are using three vectors: DNA plasmid and two disabled viruses, known as MVA and FP9. Each of these constructs contains a gene encoding portions of proteins (epitopes) from the malarial parasite. Groups of volunteers are injected with a variety of different doses and combinations of the plasmid and viruses. The plasmid is delivered by intramuscular injection and the viruses by intradermal injection. Following injections, volunteers are examined for immune system responses to the malarial epitopes.

This study was notified to GTAC in July 2001. As no objections were raised, the notification was duly accepted by the committee.

SECTION 3: RESULTS FROM UK GENE THERAPY TRIALS

GTAC	STUDY TITLE	RESULTS TO DATE
001	Adenosine deaminase gene transfer in a child with severe combined immunodeficiency syndrome	Hoogerbrugge, P.M. *et al. Gene Therapy* 3; 179 (1996). One UK patient was treated with no observed improvement as a result of the gene therapy.
002	Gene therapy research for cystic fibrosis (Nasal trial)	This trial is now closed. No serious adverse event believed to be associated with the study agent was reported.
003	A pilot study of idiotypic vaccination for follicular B-cell lymphoma using a genetic approach	This trial is now closed. No serious adverse event believed to be associated with the study agent was reported.
004	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	Application withdrawn.
005	Gene therapy for metastatic melanoma: Assessment of expression of DNA constructs directly injected into metastases	Melanoma patients were given direct injections of naked plasmid DNA into skin lesions. Twenty three patients were treated with the study agent, of which twenty had progressive disease. Two patients had stable disease and one was not evaluable. There was no evidence for therapeutic efficacy, despite covering a ten-fold range of DNA concentrations. The investigators would not recommend the use of naked DNA in future.
006	The treatment of metastatic malignant melanoma with autologous melanoma cells that have been genetically engineered to secrete IL-2	This trial is now closed. No serious adverse event believed to be associated with the study agent was reported.
007	Towards gene therapy for cystic fibrosis (Nasal trial)	Gill D.R. *et al. Gene Therapy* 4; 199 (1997). Hyde S.C. *et al. Gene Therapy* 7; 1156 (2000). 12 out of 18 patients showed evidence for transgene expression following treatment with the DNA/lipid complex. No serious adverse events were reported.

GTAC	STUDY TITLE	RESULTS TO DATE
008	Gene therapy research for cystic fibrosis (Nasal trial)	This trial is now closed. No serious adverse event believed to be associated with the study agent was reported.
009	Gene therapy research for cystic fibrosis (Lung trial)	This trial is now closed. No serious adverse event believed to be associated with the study agent was reported.
010	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	This trial is now closed. No serious adverse event believed to be associated with the study agent was reported.
011	Genetic prodrug activation therapy for breast cancer	This trial is now closed. No serious adverse event believed to be associated with the study agent was reported.
012	Use of a recombinant Vaccinia virus for therapy of cervical cancer	Clinical phase of trial complete. No serious adverse events believed to be related to the study agent were reported.
012A	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat cervical intraepithelial neoplasia III	Clinical phase of trial complete. 12 patients received a total of 21 vaccinations of the study agent. No serious adverse events believed to be related to the study agent were reported.
012B	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat cervical intraepithelial neoplasia III	Clinical phase of trial complete. No serious adverse events believed to be related to the study agent were reported.
012C	Use of recombinant Vaccinia vaccine (TA-HPV) to treat vulval intraepithelial neoplasia III	The trial commenced in February 2000. Clinical phases of the trial are now complete. 18 patients were vaccinated at a single dose of the vaccine. The virus was found to be safe with no serious adverse events being reported.
012D	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat ano-genital intraepithelial neoplasia III	The trial commenced in June 2000. 12 patients with high grade ano-genital neoplasia were given a single vaccination of the study virus. Patients have now completed a six-month follow-up. No serious adverse events have been reported.

GTAC	STUDY TITLE	RESULTS TO DATE
013	A proposal to study the efficacy of transplantation of autologous retroviral transduced bone marrow in patients homozygous for the W402X mutation (Hurlers syndrome)	Three patients with Hurlers syndrome were treated with gene-modified bone marrow transplant. While therapeutic transgene was detected in patients, its expression was short-lived. Evidence for an immune response against the transgenic protein was detected.
014	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	Ganly, I. *et al. Clin. Cancer. Res.* 6; 798 (2000). Twenty-two patients were treated in this study by single injection into a tumour of the head or neck. There was no serious adverse event related to the study virus and evidence of efficacy in five patients.
014A	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	Nemunaitis, J. *et al.* Cancer Res. 60; 6359 (2000). Khuri, F. *et al Nature Medicine* 6; 879 (2000). Thirty seven patients were treated with five daily injections of the virus in conjunction with cisplatin and 5-fluorouracil infusion over five days. The treatment was well-tolerated with an overall response rate of 63% compared to 35% for chemotherapy alone. Based on these data, a phase III trial has commenced in the US.
014B	Phase I, open-label, dose-escalation trial of intraperitoneal injection with an E1B attenuated Adenovirus in patients with recurrent/refractory ovarian carcinomas	This trial is now closed. No serious adverse event believed to be associated with the study agent was reported.
015	Towards gene therapy for cystic fibrosis (Nasal trial)	This trial is now closed. No serious adverse event believed to be associated with the study agent was reported.
016	Phase I study in patients with recurrent metastatic squamous cell carcinoma of the head and neck using SCH 58500 (rAd/p53)	Trial never commenced in the UK.
017	Gene therapy for cystic fibrosis. Delivery to nasal epithelium and lung by nebulisation of the pCFICFTR/#67	Alton, E.W.F.W. *et al. The Lancet* 353; 947 (1999). This study is complete. Eight patients were treated. Correction of the chloride defect in lungs of patients was observed. No serious adverse events were reported.

GTAC	STUDY TITLE	RESULTS TO DATE
018	A phase I dose-escalation study of intratumoral injection with modified HSV Type I (ICP 34.5) into primary and recurrent malignant glioma	Nine patients were recruited, involving seven glioblastomas, one anaplastic astrocytoma and one oligodendroglioma. HSV1716 was injected directly into the recurrent tumours using a multi-point injection technique (up to 10 injections per patient). No serious toxicity has been reported. Three patients remained alive up to 40 months post-treatment.
018A	A phase I dose-escalation study of intratumoral injection with modified HSV Type I (ICP 34.5) into primary and recurrent malignant glioma	Twelve patients were injected with HSV1716. All proceeded to tumour resection and eleven have received further anticancer treatment post operatively. There were eleven glioblastomas and one anaplastic astrocytoma. None showed evidence of toxicity. Eight patients remained alive up to 40 months post-treatment.
018B	A study of the safety of the modified Herpes simplex virus (HSV1716) when injected into tumour bearing brain following resection of recurrent or newly diagnosed high grade glioma	This study is still underway. The virus HSV1716 is injected into the brain cavity after resection of the tumour. The patients then proceed to treatment with either chemo- or radiotherapy. By 2001, eight patients had been enrolled into the study without evidence of toxicity from HSV 1716.
019	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)	Application withdrawn.
020	A clinical trial with Ad-5CMV-p53 vector in patients with malignant ascites formation	No serious adverse events thought to be associated with the study agent have been reported.
021	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 IL-2 (TG1031)	Fourteen patients with advanced breast cancer were given the study agent, derived from Vaccinia virus. No serious adverse events believed to be related to the study agent were reported. Patient enrolment stopped in March 1999.
022	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	No serious adverse events associated with the study agent have been reported.

GTAC	STUDY TITLE	RESULTS TO DATE
023	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)	No serious adverse events thought to be related to the study agent have been reported.
024	A phase I study of intraperitoneal administration of a replication deficient Adenovirus carrying a nitroreductase gene in ovarian cancer patients	No serious adverse events have been reported.
025	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	Application withdrawn.
026	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	MacKie, R.M. *et al.* *The Lancet* 357; 525 (2001). Five patients with melanoma were injected with the study virus. Two received one injection, two received two injections and one received four injections. Evidence for viral replication in tumour cells was reported. No serious toxicity was observed.
027	The use of MetXia-P450 for the treatment of advanced breast cancer (phase I/II intratumoral)	The study virus was used to treat patients with either breast cancer or malignant melanoma. Patients received either 2 or 4 injections of escalating doses into single or multiple lesions. A total of 32 doses of the virus were administered. No serious adverse events were reported.
028	A phase I/II study of hepatic artery infusion with WTP53-CMV-AD in primary metastatic malignant liver tumours	Application withdrawn.
029A	A phase I/II pilot study of idiotypic vaccination for follicular B-cell lymphoma using a genetic approach (i.m.)	This trial is ongoing. Seventeen patients had been treated with the study vaccine by the end of 2001. No serious adverse events have been reported.
029B	A pilot study of donor idiotypic vaccination for the purpose of targeted post-transplant immunotherpay following allogenic bone marrow transplantation for multiple myeloma	By the end of 2001, four stem cell donors had been vaccinated with the study agent, without any serious adverse event.

GTAC	STUDY TITLE	RESULTS TO DATE
029C	Phasel/II study of idiotypic vaccination for multiple myeloma using a genetic approach (MMIFTT)	This trial has not yet commenced.
029D	Phase I/II study of idiotypic vaccination for chronic lymphocytic leukaemia using a genetic approach (CLLIFTT)	By the end of 2001, one patient had been treated with no serious adverse events reported.
030	Use of a retrovirus carrying human cytochrome p450 for the treatment of ovarian cancer (phase I intra-abdominal)	A total of 6 injections of the study virus in conjunction with carboplatin chemotherapy was delivered to each of six patients. No serious safety issues were reported.
031	Gene directed enzyme prodrug therapy for the treatment of head and neck cancer (phase I intratumoral)	This trial commenced in 2001. One patient has been treated thus far, without any safety concerns.
032	Gene directed enzyme prodrug therapy for the treatment of liver cancer (phase I intratumoral)	The trial is ongoing, having commenced in June 2000. Twelve patients have been dosed at increasing concentrations of the study Adenovirus. No serious adverse events believed to be related to the study agent were reported. There has been no evidence of toxicity.
033	Phase I trial of immunotherapy with Adenovirus-interferon in malignant melanoma (intratumoral)	No serious adverse events believed to be related to the study agent, an Adenovirus, were reported. The trial was discontinued in May 2000.
034	A phase II/III trial of chemotherapy alone versus chemotherapy plus Adp53 in ovarian and primary intraperitoneal cancer (intraperitoneal)	One patient was recruited to the chemotherapy alone arm. The trial has now closed.
035	Phase II trial of pre-operative intratumoral injection with an E1B attenuated Adenovirus in patients with resectable head and neck tumours	Fifteen patients were treated with the study virus with a single injection into tumours. Preferential replication of the virus in tumours, especially mutant for p53, was shown. No serious toxicity was reported.
036	The safety and effects of Ad5.1 mediated human FGF-4 gene transfer in patients with peripheral arterial occlusive disease (PAOD) Fontaine stage III (phase I i.m.)	Trial in progress. No serious adverse events believed to be related to the study agent have been reported.

GTAC	STUDY TITLE	RESULTS TO DATE
037	A phase III study of quadruple HAART followed by double-blind randomisation to HIV vaccination with ALVAC-HIV and Remune or placebo	This trial is taking place in nine countries across Europe. A total of one hundred and forty five patients will be recruited. In the UK, ten patients had received the experimental vaccine by the end of 2001. Sixty nine patients had been vaccinated from all countries. Although in two cases, a relationship between the study agent and both serious adverse events could not ruled out, no serious adverse event has been definitively linked to the study vaccine.
038	A phase I, open label, dose escalation trial to assess the safety and immunogenicity of DISC-GMCSF in patients with mestatatic melanoma	The trial commenced in September 2000. A total of 19 vaccinations were administered to ten patients. No serious adverse events have been reported which are believed to have been caused by the study agent.
039	Gene therapy protocol for the evaluation of the safety, biodistribution and efficacy of TroVax in patients with metastatic colorectal cancer (phase I i.m.)	The study virus, a modified Vaccinia virus, has been administered at three different doses to patients with metastatic colorectal cancer. Fourteen patients have received 45 injections. No serious adverse events have been reported that are believed to be related to the study virus.
040	A phase I dose escalation trial of an E1B attenuated Adenovirus as an intravesical therapy for recurrent superficial/muscle invasive bladder cancer	No serious adverse events have been reported where the study agent is believed to be responsible.
041	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.)	Application withdrawn.
042	Phase I study of melanoma poly-epitope DNA and melanoma poly-epitope modified Vaccinia Ankara in patients with melanoma	Fourteen patients were treated with the study agents, naked DNA and a modified Vaccinia virus. No serious adverse events thought to be caused by the study agents have been reported.
043	A phase I/II trial of polyHER2neu-a polyepitope DNA vaccine encoding HER-2 epitopes in the treatment of epithelial cancers (i.m.)	Application declined.
044	Treatment of leukaemic relapse after allogeneic stem cell transplantation by HSV-tk transduced donor lymphocyte transfusions.	Trial in progress. No serious adverse events believed to be related to the study agent have been reported.

GTAC	STUDY TITLE	RESULTS TO DATE
045	Phase I clinical gene therapy protocol for X-SCID	Three children and one adult have been treated with the study virus. Their immune systems have been reconstituted. No serious adverse event have been reported.
046	Phase I gene therapy protocol for X-CGD	Trial in progress. No serious adverse events believed to be related to the study agent have been reported.
047	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	Trial has not commenced in the UK.
048	A randomised phase I trial of intravenous CI-1042 with or without Entanercept in patients with metastatic carcinoma	Application withdrawn.
049	A phase I/II study of immunotherapy for patients with metastatic melanoma using dendritic cells transfected with a plasmid encoding two melanoma antigens	Trial in progress. No serious adverse events believed to be related to the study agent have been reported.
050	A phase II trial of preoperative intratumoural injection with HSV1716 in patients with resectable squamous cell tumours of the head and neck	Trial in progress. No serious adverse events believed to be related to the study agent have been reported.
051	A European and Canadian multicentre, randomised, double-blind, placebo controlled study to evaluate the efficacy and safety of Ad5FGF-4 in patients with stable angina	Trial in progress. No serious adverse events believed to be related to the study agent have been reported.
052	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	Trial in progress. No serious adverse events believed to be related to the study agent have been reported.
053	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 antirctroviral therapy	Trial in progress. No serious adverse events believed to be related to the study agent have been reported.

GTAC	STUDY TITLE	RESULTS TO DATE
054	A phase II, randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of NV1FGF in patients with severe peripheral arterial occlusive disease	Trial in progress. No serious adverse events believed to be related to the study agent have been reported.
055	Gene directed enzyme prodrug therapy for the treatment of liver cancer (phase I intratumoral)	Trial in progress. No serious adverse events believed to be related to the study agent have been reported.
056	A phase II, multicentre, double-blind, placebo-controlled, dose-finding study of ZYC101a in the treatment of high-grade squamous intra-epithelial lesions of the uterine cervix	Trial has not commenced.
057	A phase I, multidose study to evaluate the safety of intramuscular injections of HER-2 DNA in patients with metastatic breast cancer	This trial commenced toward the end of 2001, at which time nine patients had been recruited. No serious adverse events thought to be related to the study product had been reported.
058	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	This trial has only recently commenced.
059	TA-HPV recombinant Vaccinia virus expressing the Human Papillomavirus 16 and 18 E6 and E7 proteins: Application to amend currently approved protocol to add a clinical trial involving a prime-boost strategy of TA-CIN administered in association with TA-HPV in high grade ano-genital intraepithelial neoplasia (AGIN) patients (PB-HPV/01)	This trial commenced in August 2001. Patients have vuval, vaginal or anal intraepithelial neoplasia. By the end of 2001, ten patients had been enrolled in the study. No serious adverse events believed to be related to the study agent have been reported.
060	Study of transfection efficacy and safety of MetXia-OB83 in patients with cutaneous lesions of breast cancer or melanoma	Trial in progress. No serious adverse events believed to be related to the study agent have been reported.
061	An upward titration study of transfection efficacy and safety of MetXia-OB83 in patients with adenocarcinoma of the prostate	Trial in progress. No serious adverse events believed to be related to the study agent have been reported.
062	First administration to man of an oncolytic Herpes virus vector containing a transgene for granulocyte macrophage colony stimulating factor (OncoVex^{GM-CSF}) – A study of its safety, biodistrubution and biological activity	Trial in progress. No serious adverse events believed to be related to the study agent have been reported.

GTAC	STUDY TITLE	RESULTS TO DATE
063	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	Trial has not commenced.
064	A phase I trial of replication-competent Herpes simplex virus (ICP 34.5 null mutant 1716) in patients with inoperable malignant pleural mesothelioma	Trial in progress. No serious adverse events believed to be related to the study agent have been reported.
065	A phase I trial of PolyMEL, a polyepitope DNA vaccine in the treatment of metastatic melanoma patients	Trial has not commenced.
066	A recombinant Vaccinia Ankara (MVA)-based vaccine encoding Epstein-Barr virus target antigens: A trial in helathy volunteers	Trial in progress. No serious adverse events believed to be related to the study agent have been reported.
067	Percutaneous intramyocardial gene therapy against myocardial ischaemia with phVEGF-A165SR – A double-blind placebo controlled study	Application pending.
068	A phase I trial of polyHER2neu – a polyepitope DNA vaccine encoding HER-2 epitopes in the treatment of breast cancer	Trial has not commenced.
069	A phase I/II study of DNA vaccination against a CMV/FrC of tetanus toxin fusion gene in allograft donors and recipients	Trial has not commenced.
071	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	Application pending.
072	Phase I/II study to determine the optimum dose and dosing regimen then to assess the efficacy of a poly-epitope pharmaccine (therapeutic vaccine), involving pSG2.Mel3 and MVA.Mel3, in patients with stage III or stage IV metastatic melanoma	Trial has not commenced.
073	Phase I clinical gene therapy protocol for adenosine deaminase deficiency	Trial has not yet commenced.

SECTION 4: REGULATORY ISSUES:

THE EUROPEAN CLINICAL TRIALS DIRECTIVE

The Clinical Trials Directive (CTD) was published on 1 May 2001. Member states have until 1 May 2003 to draw up national legislation implementing the Directive which must come into force by 1 May 2004.

The CTD approximates laws and regulations relating to the implementation of Good Clinical Practice (GCP) in the conduct of clinical trials. GCP is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials.

The CTD places strict time limits in which Ethics Committees must deliver their opinions on applications to conduct clinical trials (maximum of 60 days with no extension). However, for gene therapy applications extensions of 30 days are permitted with a further 90-day period if further consultation is necessary (total of 180 days). Under the CTD a single ethical opinion on a given clinical trial is required.

Under the current arrangements researchers must apply to the MCA for approval for the use of a medicinal product in a clinical trials setting. Those studies with commercial sponsorship must apply for a Clinical Trials Exemption (CTX). Academic researchers without the backing of a commercial sponsor are dealt with under the Doctors and Dentists Exemption (DDX). By May 2004 the CTX/DDX scheme will disappear and identical data sets will be required in support of all trials, demonstrating production to Good Manufacturing Practice (GMP) standards regardless of sponsorship status.

GTAC will continue to operate as the National Ethics Committee for gene therapy studies. Updated GTAC guidance notes will be published following implementation of the Directive taking account of these legislative changes.

SECTION 5: GUIDANCE UPDATE

THE STATUS OF GTAC AS A RESEARCH ETHICS COMMITTEE

GTAC has published recent guidance to researchers wishing to conduct gene therapy in the UK [7]. As mentioned in Section 4, GTAC will publish updated guidance when national legislation translating the European Clinical Trials Directive into law takes place. It is the intention that GTAC will be recognised as the UK wide REC for gene therapy clinical research under the new legislation. In the meantime, GTAC remains the National Research Ethics Committee for gene therapy, with its approval having equivalent status to MREC approval.

THE SUITABILITY OF GENE THERAPY RESEARCH SITES

Criteria for the suitability of gene therapy research teams and sites are covered in *Part G* of GTAC's guidance to researchers, published in our Seventh Annual Report [7]. However, as gene therapy moves increasingly from studies involving single research centres to multi-centre studies, all study centres should have appropriate measures in place to satisfy GTAC's research site requirements. In particular, Standard Operating Procedures (SOPs) should be written in advance of trials and freely available to research staff. In addition, a clinical microbiologist, who is familiar with the study agent, should form part of the wider research team. The clinical microbiologist should be able to frame any risks from the study agent in the appropriate context. This person should be able to advise on drafting of the SOPs, explain microbiological issues to the staff and provide counsel in the event of mishap.

SECTION 6: GTAC PUBLIC WORKSHOP: "GENE THERAPY FOR INHERITED DISORDERS."

PUBLIC HEALTH LABORATORY SERVICE, COLINDALE. 2 MARCH 2001.

THE WORKSHOP

Whilst there has been a significant increase in the number of gene therapy clinical trials conducted in the UK in the past few years, the vast majority of research has been aimed at cancer treatment. However, more recently, a number of high profile reports have indicated that gene therapy can be effective in treating some of the inherited monogenic disorders, such as Haemophilia-B or X-linked Severe Combined Immunodeficiency.

The "Gene Therapy for Inherited Disorders" workshop was designed to examine these latest advances in the treatment of genetic disease, to discuss possible future directions in gene therapy research and encourage dialogue and debate amongst all interested parties: from scientists and clinicians to ethicists and patient groups. As well as presentations from invited speakers, attendees participated in focussed discussion groups to examine specific issues in current gene therapy research. Summaries are provided below.

BIOGRAPHIES OF THE SPEAKERS

Professor Norman C. Nevin

Norman C. Nevin is Professor of Medical Genetics, Queen's University of Belfast and Head of the Northern Regional Genetics Service. He has held the positions of Secretary, Vice-President and President of the UK Clinical Genetics Society as well as serving on various national and international committees, notably the Human Genetics Advisory Commission. He is a member of the European Concerted Action for Congenital Abnormalities. Professor Nevin was a founder member of the UK Gene Therapy Advisory Committee (GTAC) and is currently its Chairman. His research interests have resulted in over 300 peer reviewed publications on various aspects of genetics, especially single gene disorders and congenital abnormalities.

Dr Katherine High

Katherine High graduated from Harvard with a degree in Chemistry before carrying out her M.D. studies at the University of North Carolina (UNC) School of Medicine. She then trained as a Fellow in the Hematology Section at Yale University School of Medicine for four years, before returning to UNC as a faculty member in the Department of Medicine and the Curriculum in Genetics. Later, she moved to Philadelphia to her present concurrent positions as Director of the Research in Hematology at The Children's Hospital and William H. Bennett Professor of Pediatrics and Pathology at the University of Pennsylvania.

Her research interests have focused on the molecular genetic basis of and development of novel therapeutics for haemophilia. She has published numerous scientific articles, including one of the first reports that gene therapy could be used to successfully correct an inherited disorder. She is an active member of the American Society of Hematology, the National Hemophilia Foundation and the Program Committee on Genetic Diseases of the American Society of Gene Therapy. She has also served on the editorial boards of the American Journal of Hematology, Human Gene Therapy and Molecular Therapy.

Dr Alain Fischer

Alain Fischer received his MD and PhD degrees before training as a postdoctoral researcher at University College London with Professors Beverley and Feldmann on human antigen specific T-cell clones. He later became Professor of Paediatric Immunology at Necker Hospital in Paris and is now Head of the Paediatric Immunology and Haematology Clinical Unit. He also heads the INSERM Research Unit "Normal and Pathological Development of the Immune System". His research interests include primary immunodeficiencies, genetics of immunological disorders and gene therapy.

He has served as President of the Immunology Committee at INSERM, currently is a gene therapy adviser and member of the scientific committee of Association Française contre les Myopathies and an adviser for medical research at the Ministry of Research. He is also President of the scientific committee of Fondation de la Recherche Medicale. He has received awards from the NRJ Fondation-Institut de France and the Pierre Royer Prize. His recent publication in *Science* on effective gene therapy for X-SCID has been received as a seminal breakthrough in the field (Cavazzana-Calvo *et al.*, 2000).

Dr Deborah Gill

Deborah Gill is a member of the recently-formed UK Consortium for Cystic Fibrosis Gene Therapy and works in the Nuffield Department of Clinical Laboratory Sciences at the University of Oxford, developing a gene therapy for cystic fibrosis lung disease.

Deborah has a PhD from Warwick University where she was involved in the initial discovery of the ABC (ATP-Binding Cassette) super-family of membrane proteins. Following post-doctoral work she moved in 1990 to the Institute of Molecular Medicine in Oxford to work on two human members of the super-family, the multi-drug resistant P-glycoprotein and the CFTR protein responsible for Cystic Fibrosis. Since 1993 Deborah has designed, instigated and published the results of two clinical trials of gene therapy for cystic fibrosis.

Ian Muchamore

Ian Muchamore is Senior Project Manager for Consultation and Research in the Medicine in Society Programme at the Wellcome Trust. He was trained as a geneticist and developmental biologist before moving into the Public Understanding of Science area where he has been active for the last eight years. In that time he has developed educational initiatives including exhibitions, a hands-on DNA based workshops for schools and a theatre in education play which encouraged students to discuss the social and ethical issues raised by genetic testing. He has organised many public debates and policy discussions. This work has been underpinned by the commissioning of rigorous social research to explore public opinion and attitudes. Previous studies have explored wider public perceptions of human cloning and stem cell technologies, embryo screening and prenatal testing, and gene therapy in different contexts.

PRESENTATION ABSTRACTS

KEYNOTE PRESENTATION: Trials & Tribulations

***Professor Norman C Nevin**, GTAC Chairman.*

Several thousand single gene disorders have been described; most of them are rare. Many result in serious illness and where there are conventional treatments these may be inadequate or burdensome. The prospect of somatic gene therapy (providing working copies of defective genes in those cells which need it for their proper function) is attractive if it can cure or alleviate disorders that impact so greatly on the patients' lives.

Although gene therapy emerged as a potential treatment for genetic disorders, in practice the majority of protocols world-wide have aimed to harness its' potential for the treatment of cancer. As we reach the end of this first decade of gene therapy research, encouraging evidence of positive clinical results have emerged from trials and there has been a resurgence of interest in applying gene therapy approaches to treatments for inherited disorders.

This presentation will look back at the brief history of gene therapy research and examine some of the many and varied approaches that have been developed to improve gene delivery, gene targeting and patient safety. It will also look to the future and ask whether gene therapy is showing signs that it may fulfil its enormous potential.

In order to fulfil that potential gene therapy clinical trials must continue to be conducted to the highest scientific and ethical standards with patient welfare and safety being paramount. The Gene Therapy Advisory Committee (GTAC) is the UK advisory body, established by Government and charged with the oversight of the conduct of gene therapy. The work of the Committee, including its remit, mode of working and recent important initiatives will be discussed in the context of current developments in human gene therapy.

AAV-Mediated Gene Transfer for Hemophilia B

Mark Kay, Roland Herzog, Valder Arruda, Catherine Manno, Amy Chew, Linda Couto, Alan McClelland, Bertil Glader, ***Katherine High***

We have been working to establish an experimental basis for a gene transfer approach to treating hemophilia. Using an adeno-associated viral vector (AAV) expressing Factor IX introduced into skeletal muscle, we have shown in mice and in hemophilic dogs that we can achieve long-term (>3 years) expression of clotting factor at levels that would result in an improvement in clinical symptoms of the disease. A phase I trial of intramuscular injection of AAV-F.IX has been initiated to evaluate the safety of this procedure in patients with severe hemophilia. To date, eight subjects have been enrolled at three doses, ranging from 2×10^{11} vector genomes/kilogram (vg/kg) to 2×10^{12} vg/kg. There has been no evidence of local or systemic toxicity in any of the subjects, including no evidence for inhibitor formation or for inadvertent germline transmission of vector sequences. Muscle biopsies have shown unequivocal evidence of gene transfer and expression by PCR, Southern blot, and immunohistochemistry. Some subjects have shown evidence of circulating F.IX levels above baseline, >1% but <2%, and have had concomitant decreases in clotting factor usage. In additional pre-clinical studies, administration of an AAV vector into the portal vein of hemophilic dogs has resulted in considerably higher circulating levels of F.IX, in the order of 5-14%, whereas delivery to skeletal muscle never resulted in levels higher than 1-2% in

hemophilic dogs. A proposed clinical trial of AAV-mediated, liver-directed gene transfer for hemophilia B is now in the late planning stages. We conclude that AAV-mediated gene transfer is a promising approach to the treatment of hemophilia B.

Gene Therapy of Severe Combined Immunodeficiencies

Alain Fischer

Gene Therapy represents an attractive strategy for a number of life threatening disorders. Severe inherited immunodeficiencies are among the best possible as (i) available treatments are partially unsatisfactory, (ii) disease related genes are known, (iii) gene product expression is likely to provide a growth advantage to corrected cells and (iv) once differentiated, T lymphocytes (the missing cell in these disorders) are long lived. By using defective retroviral vectors, relatively high efficiency gene transfer into hematopoietic progenitor can safely be achieved *ex vivo*, in the presence of cytokines such as flt-3L, SCF, MGDF and of a fibronectin fragment. Following *in vitro* and *ex vivo* (murine model) preclinical studies, we have set up a clinical trial for the X-linked form of severe combined immunodeficiency (SCID) caused by mutations of the γc gene. Five patients were enrolled. Selected CD34(+) cells from patients' marrow were *ex vivo* infected then re-infused. No adverse effects occurred with a follow-up of almost 2 years. In four patients, a complete correction of T-cell immunodeficiency was achieved which is so far sustained. Patients can therefore live normally without any form of treatment. These results provide a proof of principle for the efficacy of gene therapy based on the selective advantage provided to transduced cells. Assessment of long-term results will be required in order to know for how long the effect will persist. Extension of this form of treatment for closely related inherited disorders of the immune system can nevertheless be envisaged.

Gene Therapy for Cystic Fibrosis

Deborah Gill

Cystic fibrosis (CF) is one of the most common, serious genetic diseases in the UK. Gene therapy is being considered as a possible treatment for CF lung disease, which is the major cause of mortality in CF individuals. We have focused on a non-viral gene transfer vector in which plasmid DNA is complexed with cationic liposomes. Two double-blinded clinical studies, each involving 12 CF patients, in which a gene transfer formulation was administered to the nasal epithelium have been completed by our group. These studies aimed to test the safety and efficacy of single (Gill *et al.*, 1997) and multiple doses (Hyde *et al.*, 2000). The results showed no evidence of inflammation, toxicity or an immune response towards the DNA/liposomes or the CF protein. Nasal epithelial cells were collected after each of three doses for a series of efficacy assays to measure vector DNA and mRNA, CFTR protein, bacterial adherence, and halide efflux *ex vivo*. Airway ion transport was also assessed *in vivo* throughout the studies. In the first single-dose study, gene transfer was detected in six of the eight treated patients, although the gene transfer was modest and transient, indicating that repeated administration is likely to be required for long-term gene expression. In the second, repeat-dose study patients were required to attend the out-patient clinic on more than 20 occasions throughout the 4 month study period. The results showed that DNA/liposomes could be successfully re-administered to the nasal epithelium without apparent loss of efficacy. In conclusion, these studies and many others have demonstrated proof of principle for CF gene therapy. Current research is now focused on improving the efficiency and duration of CF gene transfer in the lung.

Gene Therapy: Building a Public Dialogue

Ian Muchamore

The Gene Therapy Consultative Panel was funded by the Wellcome Trust and was a collaboration between the Trust and the National Centre for Social Research. The research followed the knowledge and attitudes of a randomly selected sample of the British public over a one year period. Public attitudes towards gene therapy are more complex than previous research has been able to explore. Public optimism is very high about progress in gene therapy research and many people assume the technology is already in use. More people say they are hopeful about discoveries into human genes than say they are worried about them, although their list of worries is longer and more wide-ranging than their hopes. People make important distinctions between medical and non-medical applications, and between somatic, germ-line and *in utero* gene therapy. Initially there is widespread support for somatic gene therapy for single gene disorders such as cystic fibrosis with only a slightly lower level of support for a germ-line approach. Opportunities to learn more about the science, hear different arguments and discuss the issues in small groups lead some members of the public to reassess their initial views. Whilst the level of support for single gene therapies was solid during these interventions attitudes towards treating other conditions fell in some cases.

DISCUSSION GROUPS

Discussion Group 1: Consent, privacy and confidentiality of patients in Gene Therapy Research

This group discussed issues surrounding patient consent and privacy in gene therapy trials. In particular, it was felt that it would be useful if there was an independently mediated consent procedure for patient enrolment. It would be helpful if there could be a person not involved in the clinical trial or treatment, who could be available for patient advice.

Secondly, the issues of conflicts of interest amongst investigators were discussed. In many cases, the lead researcher may be the practicioner directly responsible for the care of the family involved. In cases where the research was being conducted at a large centre which was being fed from other local centres, it was considered beneficial if consent could first be taken at the local hospital with the primary doctor and then more formal consent taken at the secondary centre.

It was noted that it is now mandatory in the US for an observer to be present while patient consent is being taken. It was also noted that there has recently been an increased transparency and openness around the consent procedure in the UK. While there was no wish to hamper research into rare diseases in gene therapy trials, at the same time the participants needed some protection and reassurance. It was suggested that the Wellcome Trust and other organisations would be examining such issues in the future.

Finally, the patient flagging study of GTAC was discussed. There appeared not to be much concern over issues of privacy and confidentiality for participating patients. However, some concern was voiced over the issue of flagging of patients' children up to the age of 16 years. It was suggested that re-consent may be required when examining the records of these children. On the broader issue of family involvement in consent, it was felt that in some

cases, family participation and counselling may be advantageous in cases where gene therapy may have health implications for other family members.

Discussion Group 2: Gene Therapy for Single Gene Disorders

This group commented on the fact that when GTAC first came into existence it was envisaged that the majority of research would involve single gene disorders. However, the vast majority of clinical trials using gene therapy involve cancer research. This seems largely to be an issue of funding. While gene therapy for cancers have a clear commercial value, financial returns on single gene disorders may be perceived as potentially low.

A second reason for the lack of gene therapy research into single gene disorders lies in the nature of funding for understanding the basic biology of disease. Again it was felt that funding was inadequate for research into the understanding of basic mechanisms underlying single gene disorders. In addition, whilst treatments for cancers had potentially multiple therapeutic targets, single gene disorders were more likely to yield to one form of gene therapy that will work for that particular disorder based on its biology. This has rendered single gene disorders less attractive targets for funding from industry. Given the recent successes of gene therapy research on single gene disorders, it was felt that this area of research would most likely benefit from public funding. It was also believed that such funding would have a significant potential impact on understanding and treatment of single gene disorders. In summary, there was a feeling that single gene disorders were getting a "raw deal" in terms of research.

The group suggested that as GTAC also had a role in advising ministers, it should advise ministers of the need for public funding into research on single gene disorders. There was a clear funding gap which needed to be filled.

Another issue raised was the fact that because of the rarity of many of the single gene disorders, there may be a problem in getting the number of participants required in clinical trials. It was suggested that this could be achieved via pan-European collaborations.

Finally, the ethical issues of gene therapy research were brought up. It was suggested that GTAC was stringent on safety issues surrounding techniques that were just being transferred from one disease to another. However, it was acknowledged that GTACs primary concern was with patient safety. Another ethical issue raised was the value of animal models and the choice of patient groups. In many cases animal models were unsuitable and normally human subjects that are at the "end-stage" of the disease were involved in trials. In order to prove efficacy there is perhaps a case for carrying out research in patients not so severely affected by their disease, perhaps before tissue damage has occurred. This led the group to propose that another function of GTAC should be to promote the consideration of techniques such as *in utero* gene therapy. The group felt that in this case more research needed to be invested into delivery systems.

Discussion Group 3: Issues Surrounding Gene Therapy In Utero

Surprise was expressed by this group with the results from the Wellcome study presented by Ian Muchamore, which indicated that the public showed less approval for *in utero* gene therapy than for germ-line gene therapy. Why did this get a lower rating than germ-line

therapy? It was felt that such concern was based upon the fact that *in utero* therapy would involve direct manipulation of a foetus and consequently envisaged to lead to significant danger to the unborn child. It was suggested that risks associated with germ-line gene therapy were more abstract, less tangible and appeared therefore less egregious than *in utero* therapy.

This group also recognised that an important issue associated with this form of gene therapy was prenatal screening. Where *in utero* gene therapy was an option, parents would be faced with a choice between the treatment or abortion. At present, there was a considerable amount of counselling available for parents in this situation. Exhaustive prenatal screening for genetic disorders was considered to be prohibitively expensive.

The main ethical question in this discussion related to the efficacy of such treatment. It was suggested that the metabolic diseases would be suitable targets, especially involving the liver, which was considered an easily accessible target. Other disorders open to such intervention would be neurological diseases, which could be treated before brain damage would occur. In general, it was felt that amenable diseases would have to be subject to early diagnosis, should be early onset and most importantly treatment would have to be more effective *in utero* than immediately after birth.

ANNEX A: GLOSSARY

AAV

Adeno-associated virus.

Adenovirus/adenoviral

A DNA virus, usually associated with mild upper respiratory tract infections.

DNA (deoxyribonucleic acid)

The chemical (nucleic acid) substance in chromosomes and genes in which genetic information is coded.

Chemotherapy

Treatment with chemicals that destroy cancerous tissue.

Cell

The smallest unit of living organisms. It has been estimated that the body of a human adult comprises 50 million, million cells.

Cytotoxicity

The property of being able to kill cells directly.

Ex vivo

"Outside of the body." Sometimes cells can be taken out of the patient and treated externally. Once treated, they can be returned to the patient's body.

Gene

Genes are the biological units of heredity – a sequence of DNA which codes for *protein*. It has been estimated that the human genome comprises at least 30,000 genes.

Genetic disease or disorder

Conditions which are due to defects in the genetic constitution of an individual. They may be the direct consequences of defects in single genes; or in whole chromosomes, parts of which may be lost, duplicated or misplaced; or due to the interaction of multiple genes.

Germline cell

Cells in embryonic life that become sperm in males and eggs in females and transmit genetic information to the next generation.

Herpes simplex

The virus responsible for causing cold-sores.

HSV

Herpes simplex virus.

Immune response

A specific white blood cell or antibody response to an antigen (protein).

Immunohistochemistry

A diagnostic test used to determine whether a particular protein is present or not.

Immunomodulation

The use of a drug to alter, suppress or strengthen the body's immune system.

In vitro

Experiments conducted outside of living organisms, such as in cell culture (literally "in glass").

In vivo

When experiments are performed in living organisms.

Intraperitoneal

Within the cavity that contains the abdominal organs.

In Utero

In the womb (uterus).

LREC

Local Research Ethics Committee.

MREC

Multi-centre Research Ethics Committee.

Malignant

Cells that have lost their normal control mechanisms and develop into a cancer.

Metastatic, metastases

Cancer which has spread from the site of the original tumour to other tissues/organs in the body.

PCR

Polymerase Chain Reaction. A highly sensitive test used to diagnose the presence of specific stretches of DNA.

PIL

Patient Information Leaflet.

Placebo

A dummy treatment compared to which an experimental treatment must produce better results in order to be considered effective.

Prodrug

Relatively inert compounds that can be converted to an active or toxic form.

Promoter

A short piece of DNA contiguous with a gene which controls whether or not (and at what rate) the corresponding *protein* is produced.

Protein

Proteins are essential constituents of the body that are coded for by DNA. They form the structural materials of muscles, tissues, organs, and are regulators of function, as enzymes/hormones.

Proto-oncogene

Genes which play a role in cell division. There is evidence to suggest that certain cancers are caused by activation (switching on) of these genes.

Retrovirus/retroviral vector

A type of virus used in gene therapy as a vector. Such viruses are usually animal viruses rather than agents of human disease. They are made inert so that they can enter a human cell carrying a gene for gene therapy without causing disease.

Somatic Cell

The cells which make up the body of an individual excluding the egg or sperm cells.

Southern Blotting

A diagnositc test used to determine whether a specific piece of DNA is present or not.

Stem Cell

A cell that can self renew and produce all the types of cells.

Tumour regression

A cancer that has become smaller or has completely disappeared.

Tumour suppressor gene

Such genes produce proteins to regulate the rate at which cells divide. The absence or dysfunction of a tumour suppressor gene is associated with the production of cancer cells.

Unresectable

Unable to be fully removed by surgery.

Vaccinia

A member of the family of DNA-containing viruses which also includes smallpox virus. It was the standard vaccine against smallpox.

Vector

A carrier, usually a virus or lipid, to transport foreign DNA across the cell membrane into the cell.

Virus

A protein covered DNA or RNA containing organism which is only capable of reproducing within the host cell. Some viruses cause disease, such as chickenpox or influenza. Viruses suitably modified can be used as means of delivering a gene into cells.

ANNEX B: REFERENCES

1 Gene Therapy Advisory Committee: First Annual Report January 1994-December 1994. Health Departments of the United Kingdom. London. Department of Health. 1995.

2 Gene Therapy Advisory Committee: Second Annual Report January 1995-December 1995. Health Departments of the United Kingdom. London. Department of Health. 1996.

3 Gene Therapy Advisory Committee: Third Annual Report January 1996-December 1996. Health Departments of the United Kingdom. London. Department of Health. 1997.

4 Gene Therapy Advisory Committee: Fourth Annual Report January 1997-December 1997. Health Departments of the United Kingdom. London. Department of Health. 1998.

5 Gene Therapy Advisory Committee: Fifth Annual Report January 1998-December 1998. Health Departments of the United Kingdom. London. Department of Health. 1999.

6 Gene Therapy Advisory Committee: Sixth Annual Report January 1999-December 1999. Health Departments of the United Kingdom. London. Department of Health. 2000.

7 Gene Therapy Advisory Committee: Seventh Annual Report January 2000-December 2000. Health Departments of the United Kingdom. London. Department of Health. 2001.

ANNEX C: 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 Control Agency, the Health and Safety Executive, and the Department of the Environment;

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

The Committee will have 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 D: MEMBERSHIP OF GTAC

CHAIRMAN

Professor Norman C Nevin BSc, MD, FFPHM, FRCPath. FRCPEd, FRCP
(Emeritus) Queen's University Belfast and
Belfast City Hospital

MEMBERS

Professor David Harrison BSc, MD, FRCPath, FRCP (Ed)
Department of Pathology, University of Edinburgh

Mrs Rosemary Barnes*
Chief Executive, Cystic Fibrosis Trust
Kent

Professor Ian Hart BVSC, MRCVS, PhD, FRCPath*
United Medical & Dentistry Schools of Guy's and St Thomas' Hospitals
London

Mrs Ann Hunt*
Tuberous Sclerosis Association

Professor James Neil BSc, PhD, FRSE
University of Glasgow Veterinary School

Professor Anthony Pinching DPhil, FRCP (*Resigned in March 2001*)*
St Bartholomew's and The Royal London School of Medicine & Dentistry
Queen Mary & Westfield College
London

Mrs Irene Train RGN, RM, RHV, QIDN*
Formerly Director Public Health Nursing
Clwyd Health Authority

Mr Michael Harrison
Chambers of Peter Andrews QC, London

Dr Sohaila Rastan, PhD*
SmithKline Beecham Pharmaceuticals/Ceros

Ms Caroline Benjamin RN, MSc
MacMillan Genetic Associate
Liverpool Women's Hospital Trust

Dr David Crosby OBE, FRCS, LL.M
Retired Surgeon, South Glamorgan

Professor Alex Markham, PhD
Molecular Medicine Unit, St James's Hospital, Leeds

Reverend Dr Lee Rayfield SOSc
Vicar, Maidenhead

Dr Andrew Lever FRCP, FRCP(Ed), FRCPath, F. Med. Sci.
Department of Medicine, University of Cambridge

Professor Martin Gore MB, BS, PhD, FRCP
The Royal Marsden, London

Professor Terence Hamblin MB, ChB, DM, FRCP (Lond), FRCPath
University of Southampton

Dr Michael Waterhouse MA, DPhil
Southborough,
Author and Media Producer

Ms Fiona Sandford BA
Hertfordshire,
Primary Immunodeficiency Association

* Members retired from Committee at time of publication. Details of current membership can be found on our web-pages: www.doh.gsi.gov.uk/genetics/gtac

OBSERVERS

Department of Health:
Ms Elizabeth Woodeson

Medicines Control Agency:
Dr Elaine Godfrey
Dr Brian Davis
Dr Lincoln Tsang

Health & Safety Executive:
Dr Michael Mackett

Secretariat
Dr John Connolly (Secretary)
Dr Jayne Spink
Mrs Margaret Straughan

ANNEX E: REGISTER OF MEMBERS' INTERESTS

GTAC Member	Declared interests
Professor Norman C. Nevin	None
Mrs Rosemary Barnes	Director, Association of Medical Research Charity Non-Executive, Director, Greenwich Healthcare Trust, Non-Executive Director, Greenwich Building Society (now Portman Building Society)
Ms Caroline Benjamin	Partner employed as financial accountant for, and has share options in, Evans Vaccines section of Powderject plc
Mr David Crosby	None
Professor Martin Gore	Ad hoc consultancy to Schering-Plough, Bristol Myers Squib, Aventis, Novartis, Pierre Fabre, Debiopharm and Chiron
Professor Terence Hamblin	None
Mr Michael Harrison	None
Professor David Harrison	Shares – Medical Solutions & The Forensic Institute University consultancy – Fairfield Imaging, Scottish Medicine, Quintiles Directorship – EMMS (International) and EMMS (Nazareth) – both registered charities
Professor Ian Hart	None
Mrs Ann Hunt	None
Professor Andrew Lever	Consultancy & Shareholding in SynGenix Ltd
Professor Alex Markham	Scientific Advisory Board Member of Oxagen Ltd Director of, & shareholding in, Molecular Solutions Ltd Director, Bioscience Venture Capital Trust Director, Bioconsulting Ltd
Professor James Neil	None
Professor Anthony Pinching	Infrequent consultancies with Roche, Pharmacia Upjohn, Glaxo Wellcome Travel Sponsorship from Boehringer Ingelheim and Glaxo Wellcome
Dr Sohaila Rastan	Employee of Smithkline Beecham Pharmaceuticals Holder of Smithkline Beecham shares & share options Founder of Ceros
Reverend Lee Rayfield	None

Ms Fiona Sandford	Shares in Australian Mutual Provident
Mrs Irene Train	None
Dr Michael Waterhouse	None
Dr John Connolly	Spouse employed as Scientific Advisor on HIV by Bristol-Meyers Squibb

ANNEX F: EXTERNAL EXPERT ADVISERS TO GTAC

- Professor John Arrand, Paterson Institute for Cancer Research, Manchester.
- Professor Jon Austyn, John Radcliffe Hospital, University of Oxford.
- Sir Roy Calne, University of Cambridge.
- Professor James Carmichael, University of Nottingham.
- Dr Keith Channon, The John Radcliffe Hospital, Oxford.
- Professor Judith M. Chessells, Institute of Child Health, London.
- Dr Jean-Marc Collombert, Imperial School of Medicine, London.
- Professor Cotter, St Bartholomew's & Royal London School of Medicine.
- Professor Alan Craft, Royal Victoria Infirmary, Newcastle-Upon-Tyne.
- Professor David Crossman, Northern General Hospital, Sheffield.
- Professor A. Dalgleish, St. George's Hospital Medical School, London.
- Professor Kay Davies, University of Oxford.
- Professor J George Dickson, Royal Holloway College, University of London.
- Professor John A Dodge, CBE, Dept of Child Health, Singleton Hospital, Swansea.
- Professor M Dowsett, The Royal Marsden NHS Trust, Fulham Road, London.
- Professor John Goldman, Imperial College of Medicine, Hammersmith Hospital, London.
- Professor Farzin Farzaneh, The Rayne Institute, London.
- Professor John Goldman, Imperial College of Medicine, Hammersmith Hospital, London.
- Dr R Gopal, Pulbic Health Laboratory Services, Colindale.
- Professor Robert Hawkins, Christie CRC Research Centre, Manchester.
- Dr Tim Helliwell, University of Liverpool.
- Dr Simon J Hollingsworth, The Royal Free & University College London Medical School.
- Dr S Howie, Dept of Pathology, University of Edinburgh.
- Dr Charles Lacey, Imperial College School of Medicine, London.
- Dr JA Ledermann, The Royal Free & University College London Medical School.
- Professor Nick Lemoine, ICSM at Hammersmith Hospital, London.
- Professor R Leonnard, ICRF Medical Oncology Unit, Edinburgh.
- Dr Keith N Leppard, University of Warwick, Coventry.

- Professor P Lowenstein, University of Manchester.
- Professor D Lowrie, National Institute of Medical Research.
- Dr Michael Marber, The Rayne Institute, St. Thomas' Hospital, London.
- Dr David Miles, Guy's Hospital, London.
- Professor AC Minson, University of Cambridge.
- Professor Neil McIntyre, Royal Free Hospital, London.
- Dr David Mutimer, The Queen Elizabeth Hospital, Birmingham.
- Dr Nikolai V Naoumov, University College London.
- Professor ES Newlands, Imperial College of Science, Technology & Medicine, London.
- Professor Peter O'Hare, Marie Curie Research Centre, Surrey.
- Professor M Partridge, Kings College Hospital, London.
- Dr G Poston, Royal Liverpool Hospital.
- Dr CM Preston, MRC Virology Unit, Glasgow.
- Professor MA Richards, St. Thomas's Hospital, London.
- Dr S Shaunak, Hammersmith Hospital, London.
- Dr M Stanley, Dept of Pathology, University of Cambridge.
- Dr Peter Searle, CRC Institute of Cancer Studies, Birmingham.
- Professor Robert Souhami, Royal Free & University College Medical School, London.
- Dr Richard Thompson, King's College Hospital, London.
- Dr Adrian Thrasher, Institute of Child Health, London.
- Professor RA Weiss, Windeyer Institute for Medical Sciences, London.
- Professor CR Wolf, University of Dundee.
- Professor Wynford-Thomas, University of Wales College of Medicine, Cardiff.

ANNEX G: COMPENDIUM OF U.K. GENE THERAPY TRIALS 1993–2002

GTAC No.	Protocol Name	Details	Main Centres	Outline Approval	Vector	Gene	Cell line	No. of patients
001	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
002	Gene therapy research for cystic fibrosis	CF nasal trial	Royal Brompton Hospital	3-93	Plasmid	CFTR	*E.coli* DM5α	15 CLOSED
003	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 immunoglobulin	–	7 CLOSED
004	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	GIN-neo LNL-6/neo	PA317	– Trial withdrawn
005	Gene therapy for metastatic melanoma: Assessment of expression of DNA constructs directly injected into metastases	Metastatic melanoma	CRF Oxford	5-94	Plasmid	IL-2	*E. coli* JMC09	23 CLOSED
006	The treatment of metastatic malignant melanoma with autologous melanoma cells that have been genetically engineered to secret IL-2	Metastatic melanoma	Institute of Cancer Research/Royal Marsden Hospital	2-94	Retrovirus	IL-2	GP+env AM12	12 CLOSED
007	Towards gene therapy for cystic fibrosis	CF nasal trial	Oxford/Cambridge	2-94	Plasmid	CFTR	*E. coli*	18 CLOSED
008	Towards gene therapy for cystic fibrosis	CF nasal trial	Edinburgh	5-94	Plasmid	CFTR	*E. coli*	16 CLOSED
009	Gene Therapy Research for Cystic Fibrosis	CF lung trial	Royal Brompton Hospital	9-94	Plasmid	CFTR	*E. coli*	CLOSED

GTAC No.	Protocol Name	Details	Main Centres	Outline Approval	Vector	Gene	Cell line	No. of patients
010	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
011	Genetic prodrug activation therapy for breast cancer	Breast cancer	Hammersmith Hospital	10-95	Plasmid	Cytosine deaminase	*E. coli*	12 CLOSED
012	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
012A	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 & E7	MRC5	12 CLOSED
012B	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 & E7	MRC5	8 CLOSED
012C	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 & E7	MRC5	18 CLOSED
012D	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 & E7	MRC5	12 CLOSED
013	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	Main Centres	Outline Approval	Vector	Gene	Cell line	No. of patients
014	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
014A	A phase II trial of intravenous cisplatin, 5-FU and intratumoral injection with ONXY-015 into recurrent, chemotherapy naïve 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
014B	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
015	Towards gene therapy for cystic fibrosis	CF nasal trial	Oxford/Cambridge/ Leeds/Manchester Consortium	5-96	Plasmid	CFTR	*E.coli*	11 CLOSED
016	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
017	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* TG1	16 CLOSED
018	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	Main Centres	Outline Approval	Vector	Gene	Cell line	No. of patients
018A	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/Institute of Neurological Sciences, Glasgow/ Queen Elizabeth Hospital, Birmingham	7-99	HSV	ICP34.5 deleted	BHK 21/C13	12 CLOSED
018B	A study of the safety of the modified Herpes simplex virus (HSV1716) 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
019	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
020	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
021	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 IL-2 (TG1031).	Breast Cancer	Guy's Hospital, London	11-97	Vaccinia	MUC-1 IL-2	–	14 CLOSED

GTAC No.	Protocol Name	Details	Main Centres	Outline Approval	Vector	Gene	Cell line	No. of patients
022	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 HER-2/ neu	*E.coli* STBL 2	22
023	A pilot study of recombinant CEA Vaccinia virus 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	–
024	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	–	–
025	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	–	Plasmid	E1A	HEK293	– Submission withdrawn
026	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	–	5 CLOSED

GTAC No.	Protocol Name	Details	Main Centres	Outline Approval	Vector	Gene	Cell line	No. of patients
027	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
028	A phase I/II study of hepatic artery infusion with WTP53-CMV-AD in primary metastatic malignant liver tumours.	Liver cancer	Hammersmith Hospital, London		Adenovirus	p53	HEK293	– Application withdrawn
029A	A phase I/II pilot study of idiotypic vaccination for follicular B-cell lymphoma using a genetic approach (i.m.).	B-cell lymphoma	Royal Bournemouth Hospital and Royal South Hampshire Hospital, Southampton	5-99	Plasmid	Idiotypic DNA vaccination	*E.coli* JM109	17
029B	A pilot study of donor idiotypic vaccination for the purpose of targeted post-transplant immunotherapy following allogenic bone marrow transplantation for multiple myeloma	Multiple myeloma	Royal Bournemouth Hospital and Royal South Hampshire Hospital, Southampton	5-00	Plasmid	Idiotypic DNA vaccination	*E.coli* JM109	4
029C	Phase I/II study of idotypic vaccination for multiple myeloma using a genetic approach (MMIFTT)	Multiple myeloma	Royal Bournemouth Hospital and Royal South Hampshire Hospital, Southampton	4-00	Plasmid	Idiotypic DNA vaccination	*E.coli* JM109	– Trial not yet commenced
029D	Phase I/II study of idiotypic vaccination for chronic lymphocytic leukaemia using a genetic approach (CLLIFTT)	Chronic lymphocytic leukaemia	Royal Bournemouth Hospital and Royal South Hampshire Hospital, Southampton	4-00	Plasmid	Idiotypic DNA vaccination	*E.coli* JM109	1
030	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
031	Gene directed enzyme prodrug therapy for the treatment of head and neck cancer (phase I intratumoral)	Head and neck cancer	CRC Institute for Cancer Studies, University of Birmingham	7-99	Adenovirus	Nitroreductase	PER-C6	1

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032	Gene directed enzyme prodrug therapy for the treatment of liver cancer (phase I intratumoral)	Liver cancer	CRC Institute for Cancer Studies, University of Birmingham	7-99	Adenovirus	Nitroreductase	PER-C6	12
033	Phase I trial of immunotherapy with Adenovirus-interferon-γ in malignant melanoma (intratumoral)	Malignant melanoma	St. George's Hospital	7-99	Adenovirus	IFN-γ	–	1 CLOSED
034	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
035	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
036	The safety and effects of Ad5.1 mediated human FGF-4 gene transfer in patients with peripheral arterial occlusive disease (PAOD) Fontaine stage III (phase I i.m.)	Peripheral arterial occlusive disease	St George's Hospital, London	10-00	Adenovirus	FGF-4	PER-C6	–
037	A phase III study of quadruple HAART follwed 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	5-00	Canarypox	HIV-1 env, gag	AVIAN	10
038	A phase I, open label, dose escalation trial to assess the safety and immunogenicity of DISC-GMCSF in patients with mestatatic melanoma	Malignant melanona	Churchill Hospital, Oxford/ Royal Marsden Hospital, London	5-00	HSV	hGMCSF	CR2C9 (Vero-derived)	10

GTAC No.	Protocol Name	Details	Main Centres	Outline Approval	Vector	Gene	Cell line	No. of patients
039	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	14
040	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	–
041	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	–
042	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	14
043	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	–	–
044	Treatment of leukaemic relapse after allogeneic stem cell transplantation by HSV-tk transduced donor lymphocyte transfusions	Chronic myeloid leukaemia	Hammersmith Hospital, London	10-00	Retrovirus	HSV -tk	AM12	10
045	Phase I clinical gene therapy protocol for X-linked severe combined Immuno-deficiency (X-SCID)	X-SCID	Institute of Child Health, London	1-01	Retrovirus	Common gamma chain	PG13	4
046	Phase I gene therapy protocol for X-linked chronic granulomatous disease (X-CGD)	X-CGD	Institute of Child Health, London	12-00	Retrovirus	Gp91-phox	HEK293	1

GTAC No.	Protocol Name	Details	Main Centres	Outline Approval	Vector	Gene	Cell line	No. of patients
047	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	12-00	Adenovirus	HIF-1∝/VP16	HEK293	Trial not yet commenced in the UK
048	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
049	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	2-01	Plasmid complexed with peptide	MART-1 gp-100	*E. coli*	–
050	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	5-01	HSV	ICP34.5 deleted	BHK-21/C13	–
051	A European and Canadian multicentre, 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, Cambridge	5-01	Adenovirus	E1 deleted FGF-4	HEK293	–

GTAC No.	Protocol Name	Details	Main Centres	Outline Approval	Vector	Gene	Cell line	No. of patients
052	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	8-01	Vaccinia & plasmid	HBsAg	MVA: Chicken embryo fibroblasts Plasimd: *E. coli* DH5∝	–
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 antiretroviral therapy	AIDS	John Radcliffe Hospital, Oxford	5-01	Plasmid	HIV-1 clade A gag and 25 HIV-1 gag/pol/ env/nef CTL epitopes	*E. coli* DH1	–
54	A phase II, randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of NV1FGF in patients with severe peripheral arterial occlusive disease	PAOD	St. George's Hospital, London	8-01	Plasmid	FGF-1	*E. coli* XAC-1	–
55	Gene directed enzyme prodrug therapy for the treatment of prostate cancer (phase I intratumoral)	Prostate cancer	CRC Institute for Cancer Studies, University of Birmingham	4-01	Adenovirus	Nitro-reductase	PER-C6	–
56	A phase II, multicentre, double-blind, placebo-controlled, dose-finding study of ZYC101a in the treatment of high-grade squamous intra-epithelial lesions of the uterine cervix.	Anogenital neoplasia III	Hammersmith Hospital, London	11-01	Plasmid	HPV E6 & E7	*E. coli*	– Not yet commenced

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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*	9
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	8-01	Plasmid	MUC-1	*E. coli*	–
59	TA-HPV recombinant Vaccinia virus expressing the human papillomavirus 16 and 18 E6 and E7 proteins: Application to amend currently approved protocol to add a clinical trial involving a prime-boost strategy of TA-CIN administered in association with TA-HPV in high grade ano-genital intraepithelial neoplasia (AGIN) patients (PB-HPV/01)	Cervical cancer	University of Wales, Cardiff, St. Mary's Manchester; Addenbrooke's, Cambridge	7-01	Vaccinia	E6 & E7 HPV	MRC-5	10
60	Study of transfection efficacy and safety of MetXia-OB83 in patients with cutaneous lesions of breast cancer or melanoma	Breast cancer	The Christie Hospital, Manchester	7-01	Retrovirus	P450	TEFLYRD	–
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	8-01	Retrovirus	P450	TEFLYRD	–
62	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, biodistrubution and biological activity	Melanoma, breast, head & neck, cancer, non-hodgkins lymphoma	Hammersmith Hospital, London	11-01	HSV	ICP34.5-deleted ICP47-deleted Human GM-CSF	BHK 21c13	–

GTAC No.	Protocol Name	Details	Main Centres	Outline Approval	Vector	Gene	Cell line	No. of patients
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		Adenovirus	E1A conserved region 2 deleted & E3B RID gene region deleted	HEK293	– 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.	Mesothelioma	University of Glasgow	2-02	HSV	ICP34.5 deleted	BHK	–
65	A phase I trial of PolyMEL, a polyepitope DNA vaccine in the treatment of metastatic melanoma patients.	Melanoma	St James Hospital, Leeds	1-02	Plasmid	Multiple melanoma epitopes	*E. coli*	–
66	A recombinant Vaccinia Ankara (MVA)-based vaccine encoding Epstein-Barr virus target antigens: A trial in healthy volunteers	Naso-pharyngeal carcinoma	Institute of Cancer Studies, Birmingham	2-02	DNA & MVA	EBV epitopes	CEF	–
67	Percutaneous intramyocardial gene therapy against myocardial ischaemia with phVEGF-A165SR – A double-blind placebo controlled study	Coranory artery disease	Wythenshawe Hospital, Manchester		Plasmid	VEGF	*E. coli*	– Application pending
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	1-02	Plasmid	Poly epitopes of HER-2	*E. coli*	–
69	A phase I/II study of DNA vaccination against a CMV/FrC of tetanus toxin fusion gene in allograft donors and recipients	Cytomegalovirus infection following transplant	Southampton University Hospitals	6-02	Plasmid	pp65 from CMV	*E. coli*	–

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70	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		SFV	IL-12	–	– Application under review
71	Phase I/II study to determine the optimum dose and dosing regimen then to assess the efficacy of a poly-epitope pharmaccine (therapeutic vaccine), involving pSG2.Mel3 and MVA.Mel3, in patients with Stage III or Stage IV metastatic melanoma	Melanoma	University of Manchester	9-02	DNA & MVA	Multiple melanoma epitopes	CEF	–
72	Phase I clinical gene therapy protocol for adenosine deaminase deficiency	ADA-SCID	Great Ormond Street Hospital, London	12-02	Retrovirus	Adenosine Deaminase	PG13	–

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