Annual report : 2003 / Gene Therapy Advisory Committee.

GENE THERAPY ADVISORY COMMITTEE

TENTH ANNUAL REPORT

Covering the period from January 2003 to December 2003

Health Departments of the United Kingdom
2004

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The GTAC Secretariat may be contacted at:

Department of Health
652C Skipton House
80 London Road
LONDON SE1 6LH

Tel: 020-7972 1518
Fax: 020-7972 1717
Email: gtac@doh.gsi.gov.uk
Website: http://www.advisorybodies.doh.gov.uk/genetics/gtac/

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FOREWORD

Welcome to the Tenth Annual Report of the Gene Therapy Advisory Committee (GTAC) which covers the Committee's work from January to December 2003.

As the national supervisory committee for gene therapy, GTAC oversees the conduct of UK gene therapy research. It is eleven years since the first approval of a UK gene therapy clinical trial in January 1993 and, in total, GTAC has now considered 98 applications.

2003 has been another significant year for this promising branch of medicine. In June, the government announced in its Genetics White Paper its intention to spend over £10 million on funding UK gene therapy research. This speaks for the excellence of UK research in demonstrating that gene therapy has real potential. Up to £4 million was allocated to provide researchers with greater access to gene therapy vector production facilities; and another £1 million to support research into the safety of gene therapy vectors. £5.5 million was allocated to translational research on gene therapy for cystic fibrosis and other single gene disorders. GTAC looks forward to receiving novel and promising clinical trial proposals as a result of this generous support. I hope that long-term public funding will be secured and that the UK will maintain its position of leading Europe in gene therapy.

GTAC considers and advises on the acceptability of proposals for gene therapy research on human subjects, taking account of the ethics and scientific merits of the proposals and the potential benefits and risks. A major issue that carried over from 2002 was the further consideration of the two leukaemia cases in the French X-SCID trial and the implications for UK gene therapy. An important milestone were the recommendations issued in April by GTAC in association with the Committee for the Safety of Medicines on the use of retrovirus based vectors. The recommendations exemplified the workings of our regulatory framework in ensuring patient safety and the highest standards of clinical research. It is reassuring to know that all children treated with retroviral gene therapy at Great Ormond Street Hospital continue to progress well and none show any sign of leukaemia.

A second major issue was the translation into national legislation of the European Directive on Clinical Trials, and its influence on the future of UK academic clinical research. The regulations, which are due to come into force in May 2004, are expected to formalise GTAC's powers of approval and monitoring of all UK gene therapy trials. Having been involved with GTAC right from the start, I am delighted to see GTAC acknowledged in this way as the UK's authoritative voice on the safety and ethics of gene therapy.

2003 also saw the welcome formation of the British Society of Gene Therapy (BSGT) as a forum for scientific debate and networking within the UK gene therapy community. BSGT will hold its first annual meeting in March 2004 and I am sure it will be a significant event.

I was particularly delighted with the outcome of our annual public event in November, which attracted a very wide audience including Edinburgh school children. The meeting was the best attended the Committee has had so far, with five speakers who talked about public aspects of gene therapy. We are very grateful to those attendees who kindly gave us

feedback so that out next event can evolve out of the success in Edinburgh. Our next public meeting is due to take place in Cambridge on 20 July 2004, and all are welcome.

GTAC's work would not be possible without input from the wider scientific community. I wish to warmly thank all expert advisers to GTAC for their valuable, and often very rapid, contributions in response to our requests for advice. During the year, the Committee also welcomed two new members, Dr Adrian Lepper and Dr Richard Ashcroft, and wished farewell to Dr David Crosby. May I also take this opportunity to thank all GTAC members for their hard work, professionalism, and for so generously contributing their expertise.

I hope you find this report of value, and I look forward with pride and pleasure to that time in 2004 when GTAC receives its 100th application.

Professor Norman Nevin, OBE
Chairman of GTAC
March 2004

SUMMARY

In 2003, the Committee approved thirteen applications to conduct gene therapy clinical trials in the UK, which was an increase from 2002 (only seven approved applications), and close to the record years of 2000 (seventeen), and 2001 (fifteen). The Committee also approved 52 amendments to approved trials, and accepted three notifications for vaccination studies. Continuing the trend that over 70% of applications focus on **cancer**, the majority (nine) of 2003's approved applications were aimed at this disease, specifically colorectal cancer, carcinoma, melanoma, breast cancer, pancreatic cancer and advanced tumours. Three applications were an approach to combating **HIV infection**, and there was also a new application to treat X-linked Severe Combined Immunodeficiency Syndrome (**X-SCID**). Since approving the first gene therapy trial in the UK in 1993, GTAC has approved 90 gene therapy clinical trials of which four were subsequently withdrawn. The large number of applications in 2003 suggests that the UK continues to encourage and facilitate gene therapy clinical research within a carefully-balanced regulatory framework, ensuring that the UK maintains its lead position in Europe for such work. (See Section 1, 2, 3 and Annex G)

The main regulatory issue in 2003 was the consideration of the two 2002 cases in France of leukaemia linked to gene therapy treatment for X-SCID (see also Ninth Annual Report for more details). In April 2003, a **working party on retroviruses** with members of GTAC and the Committee on Safety of Medicines (CSM) produced 29 recommendations, covering pre-clinical research, vector production, vector design, ongoing studies, future approvals, monitoring, consent and serious adverse event (SAE) reporting. The second regulatory issue affecting GTAC's work was the **Clinical Trials Regulations** which will come into force in May 2004. GTAC produced a nine point response to the consultation of the draft implementing regulations. (See Section 4)

An important aspect of GTAC's work is to inform the public of research involving gene therapy by holding **annual public meetings**. The 2003 meeting in November in Edinburgh was the best-attended ever, with over 140 attendees, who heard five speakers talk about public aspects of gene therapy. The talks covered reflections on ten years of UK gene therapy, the evolution of UK gene therapy for cystic fibrosis, a parent's perspective on gene therapy for children, the ethical debates around the issues, and how the media can influence the public view of gene therapy. (See Section 5)

June 2003 saw the publication of the **Government White Paper: Our Inheritance, Our Future – realising the potential of genetics in the NHS**. This publication committed the Government to spending £50 million over three years to help fulfil its vision that the NHS should lead the world in taking advantage of the applications of new genetic knowledge for the benefit of all patients. Of the £50 million, over £10 million was specifically targeted at nurturing UK gene therapy. (See Section 6)

As with any Committee's annual report there are also a number of **Annexes**. Annex A is a glossary to help readers through some of the more technical parts of genetics, gene therapy, and clinical trials. Annex B gives brief details of the other nine GTAC Annual Reports. Annex C explains GTAC's terms of reference. Annexes D and E list the membership of GTAC and their registered interests, respectively. Annex F has a roll-call of GTAC's external advisers who have been extremely generous with their time and expertise in helping GTAC with its work. Finally, Annex G provides a summary and analysis of all UK gene therapy trials.

SECTION 1: PROTOCOLS REVIEWED BY GTAC IN 2003

In the reporting year, GTAC received fourteen new applications (GTAC 075 to 088) to undertake gene therapy clinical trials in the NHS. Of these, eleven protocols were reviewed by the Committee and three studies were approved by expedited review and Chairman's Action. One study was rejected although a modified version of the protocol was approved subsequently. The committee also received 52 applications to amend ongoing protocols (Section 2).

1.1 CANCER

Cancer is a multi-factorial disease where cells escape the body's control mechanisms and invade, erode and destroy normal tissue. The driving forces behind the development of cancer are the cell's genes which can become damaged by a variety of factors such as the environment, diet and life-style. The chance of developing cancer can also be increased by an individual's genetic make-up, for example, in the case of familial breast and ovarian cancer, where known mutations in the BRCA and other genes increase the chance of developing the disease. There are over 200 different types of cancer that can occur anywhere in the body. Surgery is usually the treatment of choice, however, cancer is less amenable to curative surgery once it has spread beyond the original tumour (metastasised). Gene therapy offers a new, yet experimental, potential treatment for cancer that could complement conventional treatments such as surgery, chemotherapy and radiotherapy. In fact, over 70% of all gene therapy clinical trials in the UK aim to develop treatment for cancer (see Figure 3, Annex G).

Nine of the ten protocols described below use an "immunotherapy" approach to cancer. Cancer cells have on their surface proteins that are not usually found on the surface of normal cells. These surface markers (tumour antigens) could provide a way for the patient's natural immune system to recognise and selectively destroy the cancer cells. However, the typical immune response of the body to cancer antigens tends to be relatively weak. Immunotherapy provides a possible way to improve the anti-cancer response by immunising patients with a gene therapy vaccine made up of cancer antigens. This approach alerts the immune system to the presence of the cancer cells, with the ultimate aim of stimulating the immune system to target and kill the diseased cells.

1.1.1 Colorectal cancer

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

GTAC 077: Gene therapy protocol for the evaluation of the safety and efficacy of TroVax in conjunction with chemotherapy in patients with metastatic colorectal cancer. The Christie Hospital, Manchester.

This study aims to immunise patients against a protein called the "oncofoetal antigen", or 5T4, found on the surface of the cancer cells. The study product, called TroVax, has been

used in an earlier phase I study (GTAC 039) which provided safety data and proof-of-principle of the therapeutic strategy. The agent is based on a virus called modified Vaccinia Ankara Virus (MVA) to which the 5T4 gene has been added. Vaccinia virus is a member of the pox virus family which was extensively used in the eradication of smallpox. Proven essentially safe and well tolerated, highly attenuated vaccinia virus strains are used frequently as the carriers (vectors) for therapeutic genes in gene therapy applications (see Figure 2, Annex G). In this study, patients receive intramuscular injections of TroVax before, during and after chemotherapy. This is to complement information from the GTAC 039 study, where TroVax was administrated after patients received chemotherapy treatment. The study was reviewed by GTAC in January 2003 and approved in February 2003.

GTAC 081: An open label study of TroVax given in conjunction with 5-Fluorouracil/ Leukovorin/Oxaliplatin: safety and immunogenicity before, during and after chemotherapy (TV2). University of Leeds, Hammersmith Hospital, London.

This is the sister study to GTAC 077. Both studies investigate the effect of TroVax when administered before, during and after standard chemotherapy treatment. Two chemotherapy regimens are used in GTAC 077 and 081. The studies aim to assess the safety and ability of the vaccine to trigger an immune response to 5T4 when used in conjunction with the appropriate chemotherapy agents. The protocol of this second arm of the study was reviewed in March 2003 and approved by Chairman's Action in May 2003.

GTAC 087: A phase II study immunologically evaluating 5T4-MVA (TroVax) in patients undergoing surgical resection of colorectal liver metastases. Christie Research Centre, Manchester.

This study of colorectal cancer also uses the TroVax study product (see GTAC 077 and 081) in patients whose colorectal cancer has spread to the liver. This phase II trial aims to evaluate the effects of the vaccine on the body's immune response, in the tumour and in blood. Intra-muscular injections of TroVax are given pre-surgery and post-surgery. The protocol was reviewed in October 2003 and approved by Chairman's Action in January 2004.

1.1.2 Carcinoma

Carcinomas are cancers of the epithelium, or skin tissue, which covers the internal and external surfaces of the body. This includes the lining of vessels and other small cavities found in skin or, more commonly, the lining of body organs, for example: breast, prostate, lung, stomach, bowel, and liver. Most cancers are carcinomas. If untreated, they tend to infiltrate adjacent tissue and to spread (metastasise) to distant organs.

GTAC 076: A phase I/II study of DNA vaccination with a CEA/pDOM fusion gene in patients with carcinomas expressing CEA. Southampton General Hospital.

This study aims to enhance the ability of the immune system to recognise a protein called "carcinoembryonic antigen" (CEA). CEA is produced by many solid tumours, including colorectal, lung, and pancreatic cancers. In this study, patients with gullet, stomach, bowel, pancreas or lung cancer, are immunised with a DNA vaccine which is engineered to produce a fragment of CEA known to stimulate the immune system (a so-called "epitope"). This is fused to a portion of tetanus toxin fragment C (FrC). FrC is non-toxic and a potent

stimulator of the immune system. It is hoped that by fusing the CEA fragment to FrC, the immune response to CEA will be boosted and that the immune system will recognise and destroy the cancer cells, including those that have metastasised to sites distant from the original tumour. The study was reviewed by GTAC in January 2003 and awarded approval in February 2003.

1.1.3 Melanoma

Melanoma is a very serious form of skin cancer. There are two main types of skin cancer, called melanoma and non-melanoma skin cancer. Melanoma, also known as malignant melanoma, is the more dangerous form of skin cancer. The main cause is exposure to intense sunlight. The number of cases of melanoma is on the increase. In the UK, there are around 40,000 new cases of non-melanoma skin cancer and around 6,000 new cases of malignant melanoma each year. Melanoma begins when the skin pigment (melanin) producing cells in the epidermal layer, called melanocytes, become cancerous. It occurs most commonly on the abdomen, head, neck or limbs. The chance of developing melanoma increases with age, but it affects all age groups and is one of the most common cancers in young adults. As with most tumours, affected cells display cancer specific proteins on their cell surface.

GTAC 080 and GTAC 086: First Administration of Dendritic Cells Transduced with ImmunoVEX$^{Tri\text{-}Melan}$ to Patients with Metastatic or Inoperable Melanoma; preliminary assessment of safety, biodistribution and indicators of efficacy. St George's Hospital, London.

This is a phase I clinical trial in patients with advanced melanoma that cannot be treated by surgery. Patients are immunised with three common melanoma-associated antigens produced by 95% of all melanomas. The carrier for the vaccine is a modified herpes simplex virus (HSV). Approximately 90% of the population are infected with HSV and so have antibodies against the virus. HSV based vectors are used in approximately 11% of protocols in the UK (Figure 2, Annex G). This study uses dendritic cells (DCs) as targets for the study product. DCs are specialised cells of the immune system whose function is to recognise foreign molecules (antigens). When DCs encounter antigens, they internalise them, break them down and export them to their cell surface as epitopes. Displayed in this way, the epitopes become visible to T-cells of the immune system which, when stimulated like this, begin to multiply and to act against cells with the foreign antigen. Here, the modified DCs are expected to stimulate T-cells to mount an immune attack against melanoma cells.

The **GTAC 080** application was reviewed by GTAC in May 2003 and declined in June 2003, primarily due to a lack of pre-clinical data. However, the applicants were invited to re-submit the study as a new protocol with additional pre-clinical data. The protocol was subsequently resubmitted as **GTAC 086**. This new protocol GTAC 086 was reviewed in September 2003 and given approval in October 2003.

GTAC 084: A phase I study of immunotherapy for patients with metastatic melanoma using dendritic cells transfected with a plasmid encoding two melanoma antigens. University of Birmingham.

As with GTAC 086, this study uses dendritic cells (DCs) as recipients of the gene therapy product. The DCs are removed from the blood of patients with late stage melanoma for

which curative surgery is not available. In the laboratory, DCs are exposed to the study product (*ex vivo*), and the modified (transduced) DC vaccine is returned to the patient by means of injections in and under the skin. The study agent is a plasmid (a piece of DNA) carrying the genes of two melanoma associated antigens. The plasmid DNA is combined with a small protein fragment (peptide) derived from influenza virus nucleoprotein to enable efficient uptake of the plasmid by the cell. The protocol is a modified version of the GTAC 049 protocol. It was reviewed by GTAC in June 2003 and approved in July 2003.

1.1.4 Breast cancer

Breast cancer usually occurs in women but it can occur also in men. It is the most common cancer in women, 30% of all cancers in women occur in the breast. Each year, there are nearly 41,000 new cases and approximately 13,100 women die from this disease in the UK. The strongest risk factor for breast cancer (apart from gender) is age, approximately 80% of all breast cancers occur after the menopause. While the number of breast cancers in women aged 25–34 has increased slightly, the risk of developing the disease in this age group remains low.

GTAC 082: Phase II trial to evaluate efficacy and safety of intramuscular injections of HER–2 DNA AutoVac™ in patients with metastatic or locally advanced breast cancer. Hammersmith Hospital, London.

Approximately 20–30% of women diagnosed with breast cancer display on their cancer cells the protein "Human Epidermal Growth Factor Receptor 2" (HER–2). The HER–2 protein is not expressed on normal cells. The study aims to enhance the ability of the immune system to recognise this HER–2 surface protein by immunising the patients with a DNA vaccine which consists of HER–2 DNA fused to two tetanus toxin fragment C (FrC) derived epitopes. These are small non-toxic FrC fragments which elicit a very strong T-cell immune response. It is hoped that by fusing HER–2 to FrC, the immune response to HER–2 will be boosted and that the immune system will recognise and destroy the HER–2 positive cancer cells. The phase I trial of this study had been approved by GTAC in September 2001 (GTAC 057). This phase II protocol was reviewed in June 2003 and given approval in July 2003. Unfortunately, the trial will not go forward in the foreseeable future due to a withdrawal of funding.

1.1.5 Pancreatic cancer

The pancreas is an organ that is located in the abdominal cavity adjacent to the small intestine. It is responsible for the production of digestive fluids and enzymes, including insulin. Pancreatic cancer is a form of carcinoma (see section 1.1.2) in the epithelial cells that form the lining of the glands in the body, called "adeno" cells. Adenocarcinoma of the pancreas is a tumour that is difficult to diagnose and to treat because it is situated deep in the abdominal cavity.

GTAC 083: A phase I/II safety study of Met-Xia-OB83 in patients with pancreatic cancer. Royal Liverpool University Hospital.

The study agent of this protocol is a replication-disabled retrovirus which is designed to affect dividing cells such as tumour cells. A derivative of the vector is also used in other GTAC

approved cancer studies (GTAC 027, 060 and 061). Retroviral vectors, which are vectors that integrate their genome into chromosomes, are used in approximately 16% of gene therapy trials in the UK (Figure 2, Annex G). The MetXia vector contains the gene for a human protein, called cytochrome P450, which is produced within cells that have taken up the study agent. Human cytochrome P450 is responsible for the breaking down of toxic chemicals in the body (detoxification). In this study, it is used as a "prodrug activating enzyme" which converts a harmless chemical (a prodrug) into an active toxic drug capable of killing cells. In theory, only those cells that have taken up the study product will metabolise the prodrug into the toxic agent. The study aims to establish the optimal doses of the study product and prodrug in patients with adenocarcinoma of the head of the pancreas. The protocol was first reviewed by GTAC in June 2003 and an amended version was re-reviewed in September 2003. This resubmitted version was approved in October 2003.

1.1.6 Multiple cancers

GTAC 088: A Cancer Research UK phase I trial of AEG35156/GEM640 (XIAP antisense) administered as a 7 day continuous intravenous infusion in patients with advanced tumours. Christie Hospital NHS Trust, Edinburgh Royal Infirmary.

Apoptosis is the term used when describing natural cell death in normally functioning cells, for example due to age or poor state of cell health. Malfunction in apoptosis is a feature of many cancers. This is thought to be due to the action of a family of proteins called "inhibitors of apoptosis" (IAP) which enable tumour cells to avoid apoptotic cell death. XIAP (X-linked inhibitor of apoptosis) is the most potent IAP and is present commonly at elevated concentrations in cancer cells. The therapeutic strategy is to reduce the amount of XIAP produced in cancerous tissue so that apoptosis of diseased cells can take place more readily. This is achieved by using a synthetic study product that binds to the gene coding for XIAP: When the cell becomes programmed to produce XIAP, a copy of the gene sequence is made (transcribed). This copy is called messenger RNA (mRNA), and, usually, it would carry the information to the protein building machinery of the cell (the ribosome) where it is decoded and "translated" into the protein. However, here, the study product binds to the XIAP mRNA. This inactivates the mRNA and blocks the production of the XIAP protein. This technology, which does not use any viral carrier or plasmid DNA, is called antisense. Unlike immunotherapy, where the immune system is stimulated to act against cancer cells, this is a direct approach to interfering with cancer genes. Here, patients with advanced or metastatic cancer refractory to conventional treatments receive the synthetic study product by infusion into a vein. The protocol was reviewed by GTAC in November 2003 and approved in December 2003.

1.2 HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

Human Immunodeficiency Virus (HIV) is the agent responsible for Acquired Immunodeficiency Syndrome (AIDS). Once a person is infected, the virus replicates and spreads through the immune system. The virus depletes cells, called CD4 T lymphocytes, of the immune system which are responsible for fighting infections. The loss of this immune system function exposes those infected to opportunistic infections. It also makes patients more susceptible to developing tumours because cells with cancerous changes are not recognised and destroyed efficiently. WHO/UNAIDS estimate that world-wide about

63 million people have been infected with the HIV virus and 22 million people have died of AIDS since the beginning of the epidemic, with approximately 3 million in 2003. In the UK, by the end of 2002, a total of almost 56,000 diagnoses of HIV infection have been reported since the epidemic began in the early 1980s.

Although Highly-Active Anti-Retroviral Therapy (HAART) has been relatively successful in treating HIV infection, it is limited by toxicity, the development of resistant forms of virus and it has significant side effects. Gene therapy may provide an alternative strategy to develop HIV prophylactic and therapeutic vaccines to enhance the immune system's response. As with most approaches to cancer, the strategy employed here is immunotherapy.

GTAC 075: A double-blind, placebo-controlled, randomised phase I study of NYVAC C in healthy volunteers at low risk of HIV infection (EV01). Imperial College London.

The study product, called NYVAC C, consists of a highly attenuated vaccinia virus strain which carries several HIV genes derived from the Clade C strain of HIV. Clade C is the predominant strain of HIV circulating in India and China. The use of vaccinia virus in the context of gene therapy is described above (GTAC 077). Healthy male or female volunteers who are HIV negative and at low risk of HIV infection receive either the NYVAC C vaccine or a placebo. It is hoped that vaccinations with NYVAC C, but not with the placebo, will elicit cellular immune responses to the HIV immunogen. The study was reviewed by GTAC in January 2003 and awarded approval in February 2003.

GTAC 085: A phase I trial to assess the safety of DNA C, and the safety and immunogenicity of DNA C followed by NYVAC C in an open, randomised comparison to NYVAC C alone in healthy volunteers at low risk of HIV infection (EV02). Imperial College London.

This study follows on from GTAC 075. Here, two study products are used. The NYVAC C vaccine of GTAC 075, which is a vaccinia virus derived vector carrying the genes for several HIV proteins, and a DNA vaccine, carrying the same genes (DNA C). It is a "prime-boost study" in two groups of patients. The rationale of this strategy is that patients can be "primed" to develop a better (boosted) response to the NYVAC C product if they receive first the DNA vaccine. Accordingly, patients receive either DNA C followed by NYVAC C, or NYVAC C only. The study aims to evaluate the safety of the treatments and compare the immune response of the prime-boost regime with that of NYVAC C given alone. The study was reviewed in September 2003 and approved by Chairman's Action in October 2003.

GTAC 079: A pilot study to evaluate the safety, tolerability and immunogenicity of a candidate HIV–1 vaccine, MVA.HIVA, delivered to HIV–1 sero-positive adults receiving HAART. John Radcliffe Hospital, Oxford.

Lymphocytes are cells in the blood that have a variety of functions, including the production of antibodies and they act to prevent viral, bacterial and fungal infections. There are specialised lymphocytes for fighting HIV and their presence in the blood is an indicator for HIV infection. These cells play a crucial role in controlling HIV replication during the early phase of infection. In this study it is hoped that therapeutic vaccination with HIV derived antigens may improve the body's defences against HIV by stimulating the production of anti-HIV lymphocytes, while viral control is maintained by means of HAART. The study uses a

vaccinia virus derived vector (see also GTAC 077) modified to produce several HIV antigens of HIV subtype A, which is the most common infecting strain in Africa. The study was reviewed by GTAC in March 2003 and awarded approval in July 2003.

1.3 IMMUNODEFICIENCIES (X-SCID)

X-linked Severe Combined Immunodeficiency syndrome (X-SCID) is an inherited disorder that affects boys rendering them highly susceptible to infections with bacteria and viruses. It is due to a faulty gene on the X chromosome. As boys have only one copy of the X chromosome, a faulty gene on this chromosome results in disease in males. In females, who have two copies of X, a single faulty X chromosome results in her being a carrier with a high risk of having affected sons. Each year, around 3 to 4 boys are born with X-SCID in the UK. In X-SCID babies, the immune system is not effective because certain types of specialised blood cells (lymphocytes), whose normal function is to fight infections, fail to develop and function properly. The lymphocytes lack on their cell surface a functional protein (encoded by the gamma-c gene) which would normally receive signals from molecules called cytokines. The correct reception and processing of these signals is essential if the cells are to develop properly into fully functional lymphocytes.

Untreated, boys with X-SCID normally die before they are 1 year old. These children can be protected from infection by isolation in sterile environments and by treatment with drugs to protect against infection whilst waiting for a bone marrow transplant. Bone marrow transplantation, or more specifically haematopoetic stem cell transplantation (HSCT), offers a cure for X-SCID. When a fully matched sibling donor (a brother or sister) is available, the chances of success are very good (90%). In this case, the tissues match closely and the transplant is unlikely to cause unwanted reactions in the recipient. However, only a third of patients have a fully matched donor and the chances of success from other donor sources, for example from non-related individuals or mismatched parents, are significantly worse. For patients where no fully matched donor is available, new treatment options are being explored. Gene therapy can offer long-term correction of the underlying genetic defect.

GTAC 078: A phase I clinical gene therapy trial for X-SCID using umbilical cord blood. Great Ormond Street Hospital, London.

Results from the on-going gene therapy study for X-SCID (GTAC 045) suggest that it is a good therapeutic alternative to transplantation from non-related individuals and mismatched parental donors. Under the GTAC 045 protocol, bone marrow is taken from the patient. Stem cells, purified from the bone marrow, are exposed to a retrovirus vector which carries the gamma-c gene, and then returned into the patient. The purpose of the GTAC 078 study is to allow for the use of umbilical cord blood. In cases where the diagnosis has been made before birth, the cord blood can be used as a source of stem cells required for the therapy. Umbilical cord blood is harvested at birth, the stem cells exposed to the vector, and then returned to the patient. The potential advantages over bone marrow gene therapy are treatment at an earlier age before onset of infection, and the avoidance of bone marrow harvest. As with GTAC 045, prospective patients are considered for entry when matched family bone marrow donors are unavailable. The study was reviewed by GTAC in January 2003 and approved in February 2003.

SECTION 2: AMENDMENTS TO ONGOING PROTOCOLS

ENROLMENT INTO RETROVIRAL VECTOR TRIALS AT GREAT ORMOND STREET HOSPITAL, LONDON

Applications to enrol new patients into the retroviral gene therapy studies at Great Ormond Street Hospital are subject to case by case assessments by GTAC. This provision has been in place since April 2003 as a precautionary measure following the announcement that two children had developed a leukaemia-like illness following retroviral X-SCID therapy in France. For further details and the recommendations of the GTAC/CSM working party on retroviruses, see also Section 4.

Three applications to treat three new patients with gene therapy at Great Ormond Street Hospital were received in the reporting year. These concerned the treatment of one patient each in the X-SCID, chronic granulomatous disease and adenosine deaminase deficiency studies (protocols GTAC 045, 046 and 073, respectively). After careful consideration of the available data, such as the severity of the disease phenotype, the clinical condition of the patients, the availability and likely outcomes of conventional treatment options for the patients, and the provision for informed consent of the parents, GTAC awarded approval in all three cases.

SUMMARY OF AMENDMENTS TO ON-GOING PROTOCOLS

In the reporting year, GTAC received 52 applications to amend ongoing studies. These are listed below.

January to February

GTAC 031: Approval to extend the dosing schedule of virus and prodrug.

GTAC 062: Approval of Amendment 6 of the study which is a multi dosing schedule in patients and to open a new study centre at Queen Elizabeth Hospital, Birmingham.

GTAC 069: Approval to open a new study site at University College Hospital London.

February to May

GTAC 051: Conditional approval of Amendment 2 of the study. Full approval of a revised amendment was given subsequently.

GTAC 075: Full approval of the trial following conditional approval in February 2003.

GTAC 072: Approval of Amendment 2 which related to clarification of protocol defined procedures.

GTAC 055: Approval of several administrative amendments.

GTAC 049: Approval of amendments to the inclusion/exclusion criteria and administrative changes.

GTAC 047: Full approval of the study following conditional approval in May 2002.

GTAC 039: Approval of Amendment 11 which related to patient numbers.

GTAC 076: Full approval of the study following conditional approval in February 2002.

GTAC 077: Full approval of the study following conditional approval in February 2002 and inclusion of Queen Elizabeth Hospital, Birmingham as a new study centre.

GTAC 029B: Approval of Amendment 4 which concerned the inclusion of University Hospital London as a new study centre as well as some administrative changes.

GTAC 045, 046 and 073 Approval to resume patient recruitment into the retroviral trials.

May to July

GTAC 032: Approval to administer a second round of study product to two individual patients.

GTAC 055: Approval for dose escalation.

GTAC 051: Approval of the Royal Infirmary Edinburgh site for patient recruitment (pre-amendment 2).

GTAC 051: Approval of the PIL for the Royal Infirmary Edinburgh site (pre-amendment 2).

GTAC 051: Conditional approval of the PIL following amendment 2.

GTAC 047: Approval of the up-dated PIL.

July to October

GTAC 051: Conditional, followed by full, approval of Amendments 2 and 3 of the study which concerned administrative changes as well as additional patient evaluation tests.

GTAC 051: Approval of Amendment 4 which concerned administrative changes.

GTAC 051: Approval of a new study centre site, the Wythenshawe Hospital in Manchester.

GTAC 051: Approval of a new study centre at the Royal Infirmary Edinburgh.

GTAC 051: Three approval letters for additional clinicians.

GTAC 051: Approval of a patient information chart.

GTAC 054: Approval of a new study centre site, the Wythenshawe Hospital in Manchester.

GTAC 054: Approval of Amendment 9 which related to administrative adjustments and amendments to the inclusion/exclusion criteria.

GTAC 054: Approval of a new Principal Investigator at Leicester Royal Infirmary.

GTAC 075: Approval of Amendment 1 which is to collect additional blood samples from patients.

GTAC 055: Approval of a new study centre, the Freeman Hospital in Newcastle.

GTAC 055: Approval to open the inoperable arm of the study.

GTAC 029: Approval of an amendment for repeat vaccinations.

GTAC 069: Approval of Amendment 4 which concerns a change to the vaccination schedule.

GTAC 060: Approval of an amended PIL which now mentions the French leukaemia cases.

GTAC 079: Full Approval of the trial following conditional approval in May 2003.

GTAC 065: Full Approval of the trial following conditional approval in January 2002.

GTAC 018B: Approval to re-treat patient 1 with a third round of treatment.

October to December:

GTAC 051: Approval of an independent cardiologist at King's College Hospital.

GTAC 051: Approval of the Nottingham City Hospital site.

GTAC 051: Approval of the Cardiff site.

GTAC 051: Approval of an independent cardiologist at Edinburgh Hospital.

GTAC 054: Approval of Amendment 10 which updates the clinical protocol and PIL with new guidance.

GTAC 032: Approval to treat 2 new patients.

GTAC 072: Approval to open a new study centre at Southampton General Hospital.

GTAC 072: Approval to amend the inclusion criteria.

GTAC 060: Approval to retreat a patient.

GTAC 062: Approval of a uniform dosing regimen for all patients.

GTAC 055: Approval to recruit an additional cohort of patients to the trial.

SECTION 3: NOTIFICATIONS TO GTAC

Three notifications for vaccination studies in healthy volunteers were received during the reporting year. The protocols were accepted by GTAC and recommended for review by the non-specialised Research Ethics Committees.

ANTI-MALARIA VACCINES

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

The current clinical vaccine development programme at Oxford uses two different viral vectors (attenuated vaccinia and attenuated avipox virus) as carriers for the gene inserts of several malaria derived epitopes. This study adds a plasmid DNA vaccine to this list to study a prime-boost regime of vaccination, similar to that described for the GTAC 085 study. GTAC was notified of this study in June 2003 and accepted the notification in July 2003.

ANTI-HIV VACCINES

Phase I study with MVA HIV–1 Clade A vaccine in healthy volunteers (IAVI #11). The John Radcliffe Hospital, Oxford.

This is an extension to the existing clinical trials programme at Oxford for prophylactic HIV vaccines in healthy volunteers. It is a dose escalation study of a vaccine based on modified vaccinia virus Ankara. The trial aims to evaluate the safety and immunogenicity of three different dosages of the vaccine given via three routes of injection. GTAC was notified of this study in August 2003 and accepted the notification in October 2003.

DNA/MVA peak cell response study in HIV uninfected healthy volunteers (IAVI #16). The John Radcliffe Hospital, Oxford.

This is the sister study to IAVI #11. It is a prime-boost study that aims to compare the T-cell responses to two existing vaccines, both of which contain the same HIV derived antigens. These are a plasmid DNA vaccine and the vaccinia virus Ankara based vaccine used in the IVAI #11 protocol. GTAC was notified of this study in August 2003 and accepted the notification in October 2003.

SECTION 4: REGULATORY ISSUES

4.1 LEUKAEMIA LINKED TO GENE THERAPY TREATMENT FOR X-SCID

In September and December 2002, reports were received by GTAC of a leukaemia-like illness in two patients enrolled in a French retroviral gene therapy study for the treatment of X-SCID. Retroviruses insert their genetic material randomly into the host genome. The insertion of the retroviral vector near the promoter of the proto-oncogene LMO2 has been linked to the observed T-cell leukaemia.[1,2] In March 2003 a joint working party of GTAC and the Committee on Safety of Medicines (CSM) met to:

- Review the current state of knowledge in relation to the risks of insertional mutagenesis (gene disruption) in retroviral gene therapy;
- Review current UK retroviral gene therapy clinical trials;
- Make recommendations in relation to retroviral gene therapy and UK retroviral gene therapy trials.

Below are the 29 recommendations endorsed by GTAC and CSM. These relate to pre-clinical research, vector production, vector design, ongoing studies, future approvals, monitoring, consent and SAE reporting.

See also: http://www.advisorybodies.doh.gov.uk/genetics/gtac/publications.htm

RECOMMENDATIONS OF THE GTAC/CSM WORKING PARTY ON RETROVIRUSES, APRIL 2003

FUTURE RESEARCH

The working party determined that there is currently little firm evidence that can be used in estimating the extent to which the risk described by the French leukaemia cases may be translated to other trials because:

- The gamma-c therapeutic gene itself may contribute to the pathogenesis of leukaemia due to its lymphocyte growth promoting activity and its over-expression in the context of the vector,
- The primary disease (X-SCID) may also predispose to the development of leukaemia by influencing retroviral vector integration near LMO2 or by another mechanism,
- The basis of selection for vector insertion into LMO2 is unknown. This could be due to preferential integration or preferential engraftment of those cells with LMO2 over-expression,

1 Williams & Baum. Gene therapy – new challenges ahead. Science, 2003, 302:400-401.
2 Hacein-Bey-Abina *et al.* LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. Science, 2003, 302:415–419.

- Small differences between the French and UK trials in vectors and packaging cell line might make a significant difference to the risk profile, although this appears unlikely on theoretical grounds,
- Other issues such as the age of child at treatment could have a major bearing on the risk of leukaemia development.

On this basis the working party recommends to the Department of Health that it commission research into the safety of retroviral vectors. The areas of research which should be prioritised are covered in recommendations 1 to 6.

RETROVIROLOGY

Recommendation 1: More fundamental research into the biology of retroviral integration should be pursued. The degree of integration preference and effects of cellular context are poorly understood.

THE ROLE OF THE TRANSGENE

Recommendation 2: *In vitro* models involving the over-expression of LMO2 in T-cells with gamma-c should be developed to address fundamental questions about the effects of such events on the biology of the cell – e.g. effects on responses to growth regulatory cytokines.

Recommendation 3: The intrinsic oncogenicity of gamma-c should be assessed in a relevant *in vivo* model. For example, the events in the recent trials could be recapitulated by retroviral delivery of the gamma-c gene to gamma-c deficient mice engineered to express an LMO2 transgene.

STEM CELL BIOLOGY

Recommendation 4: The age of the patient may have a significant influence on haemopoietic cell populations available for transduction. The question as to whether some cells are more susceptible to viral transduction and transformation should be addressed using harvested bone marrow and cord blood cells *in vitro*.

Recommendation 5: Information should be gathered in relation to natural variation in LMO2 expression during development, and the effect of X-SCID disease. Cord blood stem cells may represent a useful source of normal stem cells for this purpose.

Recommendation 6: Stem cell biology research is a major priority for several UK funding bodies at present. Some of these existing resources should be channelled to address issues pertinent to gene therapy e.g. the effects of vector/ genetic modification on integrity of stem cell function.

VECTOR PRODUCTION

Recommendation 7: The possible oncogenic contribution of endogenous mouse viruses present in vector producer cell lines needs to be formally assessed. We recommend that the possible delivery of VL30 sequences to engrafted and/or leukaemic cells should be assessed and reported from the UK and French trials.

Recommendation 8: If VL30 and similar elements cannot be excluded as risk factors, future protocols should employ human producer cell lines. Greater standardisation of these key resources is required.

VECTOR DESIGN

The working party identified a number of advances in vector design that may be advantageous to pursue in the longer-term and for future generations of retroviral vectors:

Recommendation 9: Removing the enhancer duplications from the Long Terminal Repeats of standard MLV-based vectors should be considered, as these are strongly correlated with leukaemogenic potency in the wild-type viruses.

Recommendation 10: Additional safety features should be considered including self-inactivating vectors and non-viral promoters to drive therapeutic genes.

Recommendation 11: Vectors incorporating suicide genes are already in use in some protocols, but these might have deleterious effects where long-term survival of transduced cells is required. In addition, this strategy may not be entirely effective because it is likely that not all cells will express the suicide gene. Research should continue to explore the safety and utility of established and new suicide gene vectors in animal models.

ONGOING STUDIES OF EX VIVO *RETROVIRAL GENE THERAPY*

Recommendation 12: The data currently available on long-term outcomes of haploidentical transplants in SCID patients is limited and patients remain on life-long immunoglobulin therapy. Questions remain about the likelihood of developing leukaemia-like disease post-transplant and there is also a lack of certainty about quality of life. There is currently no justification for recommending haploidentical transplantation in preference to gene therapy. Regular updates are needed with regard to the risk assessment of different transplant techniques, namely mortality, morbidity and the risk of leukaemia. It will be important to assess this on an ongoing basis for the purposes of benchmarking.

Recommendation 13: The current provisions for case by case assessments of applications to treat individual X-SCID patients with gene therapy should continue. The case by case assessments should be based on the severity of the disease phenotype, clinical condition of the patient, and the availability and likely outcomes of conventional treatment options for that patient.

Recommendation 14: In addition to examining expression profiles in patient samples, researchers treating patients in the X-SCID study should specifically monitor LMO2 and gamma-c expression.

Recommendation15: The current provisions for case by case assessments for X-SCID should be extended to encompass other gene therapy studies involving the modification of haematopoetic stem cells with retroviral vectors to treat inherited disorders.

Recommendation 16: The current provisions for case by case assessments should not be extended to UK retroviral gene therapy studies for cancers or disorders associated with cancers.

FUTURE APPROVALS

Recommendation 17: For the foreseeable future, applications of *ex-vivo* gene therapy involving the modification and transplantation of haematopoetic stem cells should be limited to life-threatening disease for which current therapy is inadequate or imposes an unacceptable quality of life on the individual.

Recommendation 18: Integration copy-number may be critical for optimal therapeutic advantage, but is likely to be positively correlated with risk. Where possible pre-clinical studies should attempt to define the optimal copy number of the treatment gene in relation to therapeutic effect and assess the likely integration copy number, using different protocols, in an appropriate cell line relevant to the *in vivo* target tissue (for example in hepatocytes where the target organ is the liver).

MONITORING OF PATIENTS ENROLLED IN EX VIVO RETROVIRAL GENE THERAPY STUDIES FOR THE TREATMENT OF INHERITED DISORDERS

Recommendation 19: Resources need to be identified to allow potential problems to be handled as and when they arise. The work that will need to be done to protect patient interests in the light of the French SAEs is of great importance and is likely to carry significant research costs.

Recommendation 20: It is fundamentally important to collect as much molecular and cellular data as possible, including documenting the insertion sites of retroviral vectors in trials world-wide. We recommend this to researchers in the wider international community.

Recommendation 21: More intensive monitoring or additional invasive procedures where treated patients are currently healthy should not be undertaken.

Recommendation 22: Monitoring and follow-up research for all patients, not only those who have gone on to develop leukaemia, is key. Resources will need to be identified to provide for the long-term monitoring of those patients already treated with *ex-vivo* gene therapy in the UK. This funding should be identified prospectively for future patients.

Recommendation 23: Patient samples should be prospectively monitored for the appearance of oligoclonal populations of T-cells as these may likely precede monoclonal populations. The development of rapid and accurate technologies to look for the site of retroviral insertion and emerging clonality is desirable.

Recommendation 24: Materials (including serum and cell samples) should be archived as a resource for future research (before, during and after therapy). Protocols for sampling, collection, processing and storage (pre and post therapy) should be standardised. Organisations should be invited to bring forward proposals for storage and access to stored materials.

Recommendation 25: The effects of immunisation and infection on T-cell clonality should be monitored in recipients of haematopoetic stem cell retroviral gene therapy.

CONSENT

Recommendation 26: Where gene therapy is determined to be an acceptable option for a given patient, the final decision in relation to whether to choose gene therapy or conventional treatment should remain with the patient / the patient's parent(s) or guardian. Appropriate information and independent, non-directive counselling will be essential in such cases. There is a clear role for patient advocacy groups in this process and we recommend that they should be intimately involved in providing advice.

Recommendation 27: Valid consent for the retention, archiving and future use of patient materials must be sought.

Recommendation 28: All UK retroviral gene therapy clinical trials should be required to refer directly to the French gene therapy related leukaemias as part of their patient information leaflets and in the process of obtaining informed consent.

SERIOUS ADVERSE EVENT REPORTING

Recommendation 29: The working party commended the openness and transparency with which information related to the serious adverse events in the French X-SCID trial had been shared with the international community. In the longer term we recommend that the Department of Health/Licensing Authority establish mechanisms to ensure that there is adequate international collaboration in the sharing of safety information from gene therapy trials.

4.2 GTAC'S RESPONSE TO THE CLINICAL TRIALS REGULATIONS

Regulations to implement the European Union (EU) Directive 2001/20/EC on Good Clinical Practice in Clinical Trials are due to come into force in May 2004. The regulations cover all aspects of the conduct within the EU of human clinical trials with medicinal products, including gene therapy agents. There are implications for a wide range of stakeholders, including researchers, industry, universities and the NHS as well as those that fund clinical trials involving medicines. The Medicines and Healthcare products Regulatory Agency (MHRA) invited all stakeholders to comment on the proposals for implementation of the directive and on the draft implementing regulations which transpose the directive into UK national law. The closing date for the consultation was 16 May 2003. Further details of the directive and the implementing regulations can be found on the MHRA website (http://medicines.mhra.gov.uk/)

In May 2003, GTAC submitted to the MHRA the following nine point response to the draft regulations of that time:

General Comments

1. The increased costs for academic clinical research are likely to be proportionately greater than for industry sponsored trials. Although this may prove problematic for the academic research community as a whole, it may in particular further disadvantage clinical research for orphan diseases where potential returns on investment are considered less favourable than returns that can be realised from developing treatments for more prevalent conditions.

2. Article 18 subsection 3 precludes the approval of any clinical trial that could potentially result in the modification of the patient's germ-line. Although data may be available for a given product that demonstrates minimal risk, absolute certainty could never be guaranteed. We would urge that the relevant section be amended to preclude the approval of trials where the intent is to modify the germ-line or where evidence exists to suggest that there is a demonstrable risk of germ-line contamination (where the subjects have child-bearing potential).

3. For clarification: There appears to be provision for the UK to inspect off-shore facilities in multi-European studies. It is not clear whether this arrangement be reciprocal with other authorities claiming the right to inspect NHS facilities. What effect would an unfavourable inspection of non-UK premises have on the UK arm of a study in the event that the UK facilities and premises meet the required standards?

4. Schedule 1, part 5 is inconsistent with English law. Under English law no one has the right to give consent on behalf of a permanently incapacitated adult. An incapacitated adult must be treated under doctrine of emergency (in the subjects presumed best interests to preserve life until the acute situation has passed) or doctrine of necessity (where the patient is terminally incapacitated and treatment is in accordance with the patient's best interests, which is generally understood as in accordance with established best clinical practice to maintain life).

Comments specific to the Regulations and Schedules pertinent to Ethics Committees

5. We note that an applicant may resubmit their protocol to a second ethics committee in the event that an unfavourable review is given by the first. This raises two issues. The first relates to the general competence of the ethics committees. If the second ethics committee contradicts the opinion of the first then which opinion takes precedent? The general provision for appeal to a second ethics committee appears to contradict the spirit of the directive in that a "single ethical opinion" should stand in a given member state. The second issue relates to ethical approvals of gene therapy studies. Given that gene therapy is not considered ordinary medical research and subject to approval by GTAC, who then amongst the general ethics committees should be considered competent to reassess these protocols? Mechanisms could be envisaged that would overcome this issue. GTAC would wish to further explore the options prior to introduction of this legislation.

6. The definitions of Lay and Expert members are extremely restrictive. For example, the interpretations of Lay and Expert members appear to exclude from either category

non-medical academics who are not involved in clinical research but whose institutions are. Clarification is required so as not to exclude such individuals whose talents and contributions are indispensable to the ethics committees.

7. The question of SOPs, at 6(3)a, implies that both the SOPs and amendments to SOPs of individual ethics committees must be approved by the appointing authority. If this is to be the case, has due consideration been given to the resources this would consume, both from the committees and the appointing authority? There also arises the question of conformity (and individuality in SOPs) and on what basis judgements about these will be made.

8. There is no requirement within the regulations for researches to report SAEs to the ethics committees. We believe that SAEs that are not related to the study product are an important component in determining the overall ethical acceptability of a study and may be central to patient safety.

9. Although there is provision for the Licensing Authority to rescind its approval and halt a clinical trial there is no corresponding provision for a REC to withdraw its approval or for the trial to be halted on ethical grounds. This is extremely unfortunate since new information pertinent to the ethical acceptability of the study may arise during its conduct. We recognise that this provision is written into Governance arrangements for RECs but we are of the opinion that it should be mirrored in the legislation.

4.3 DELIVERY AND GUIDANCE OF GENE THERAPY TRIALS IN THE NHS

In October 2003, Mrs Debbie Beirne and Professor Andrew Lever of GTAC, the GTAC Secretariat, and officials of the Department of Health and the Health and Safety Executive (HSE) met with representatives of the Institute of Cancer Studies, University of Birmingham, to discuss future strategies for delivery of gene therapy in the NHS. The meeting was chaired by Professor Lever and focussed on two main areas: strategies for gene therapy service delivery and the White Paper commitment on gene therapy vector facilities (see also Section 6).

The subject of service delivery fits in well with a number of other initiatives in the community on how to deal with gene therapy research in NHS hospitals from the point of view of the various stakeholders. A workshop aimed a developing best practise amongst UK clinical gene therapy practitioners is planned. In addition, HSE is developing guidance to help users to classify gene therapy trials and to meet the European requirements. This guidance document will be distributed to all centres dealing with GMOs for reference.

SECTION 5: GTAC PUBLIC MEETING

GENE THERAPY – CORNERSTONE OF MODERN MEDICINE IN THE NEW MILLENNIUM? EDINBURGH INTERNATIONAL CONFERENCE CENTRE, 17 NOVEMBER 2003.

The 2003 GTAC public meeting focused on public aspects of gene therapy. The meeting was planned to coincide with the 2003 European Society for Gene Therapy Annual Conference in Edinburgh. The audience of around 140 people included members of the public, patient group representatives, nurses, clinicians, academic and industry scientists, and students from Edinburgh Secondary Schools.[3]

5.1 SUMMARY

Mr Michael Harrison, GTAC lay Member, chaired the meeting. **Professor Norman Nevin**, Chairman of GTAC, gave the opening address on "reflections on ten years of UK gene therapy", which emphasised that although well over 70% of gene therapy trials have focussed on cancer, there have also been significant developments aimed at treating inherited, cardiovascular, and infectious diseases.

Mrs Rosie Barnes, Chief Executive of the Cystic Fibrosis Trust, and former member of GTAC, gave the audience a flavour of the evolution of gene therapy for cystic fibrosis in the UK. **Miss Cara Doran**, a Cystic Fibrosis Patient Advocate, spoke about the regime of medicines and exercises that need to be taken every morning, and of her experiences as a 25 year old sufferer of cystic fibrosis.

Mrs Fiona Sandford, lay member of GTAC, parent of a child born with combined immunodeficiency, and Vice President of the Primary Immunodeficiency Association, gave a parent's perspective on different treatment options for children with life-threatening immunodeficiency disorders. For many parents, the prospect of gene therapy can provide more hope than a bone marrow transplant.

Dr Richard Ashcroft, senior lecturer at the Medical Ethics Unit at Imperial College London and GTAC lay Member, outlined how ethical debates surrounding genetic modification have changed over the last decades. He suggested that a more realistic understanding of what gene therapy is will help focus the debate on the matters which are of most importance.

Dr Geoff Watts, a scientific broadcaster, gave examples of how the media can influence the public view of gene therapy technologies, how this can affect the future development of the science. He also spoke about a piece of academic research from Cardiff University on how the media portrays science.

3 See also the editorial in *Gene Therapy* (2004) 11, 427-428.

5.2 WHAT THE AUDIENCE THOUGHT OF THE PUBLIC MEETING

Feedback forms received from 58 members of the audience revealed that 59% of responders classified themselves as students, 19% as scientists and 22% as "other".

Delegates mostly rated the event as Excellent (33%) or Good (53%). 95% thought that the Government should continue to support UK gene therapy research and clinical trials. A perhaps surprisingly high number (60%) have discussed gene therapy with family and friends. 50% did not think the event had changed their perception of gene therapy (interestingly, 36% thought that it had). 67% thought that the prospects for gene therapy were good. Delegates were much less enthusiastic about media coverage, with 48% thinking it was only fair, and 22% thinking it was poor. A handful of choice comments include:

- "It may only be of benefit to 7000 people in the Government's eyes but it would have huge impacts on their lives and future generations."
- "Gives children a second chance."
- "Contact with concerned patients is essential to focus on scientific activity and its aims. It's not about the publications it's about the patients!"
- "It gave a very realistic and honest view on gene therapy as it stands today."
- "It is better for patients to have the choice even if they don't chose to use the treatment."
- "The meeting has made me more informed and positive about gene therapy and convinced that research and development in this field should continue."
- "The personal experience described by Fiona [Sandford] and Cara [Doran] brought home how important the research is."
- "Some of the information was more appropriate for a professional/scientist audience. I found this difficult to follow. A clearer outline of the aims of the morning – in terms of introduction to GTAC or to gain public views or disorder focus or current research would help the audience. However, overall a very good morning!"
- "I think it needed to be a bit more positive. The general public will dwell on the problems, for example the leukaemia cases, as they understand about cancer more than gene therapy. Needed to give examples of the whole range of diseases that are being researched. I don't think people realise the range of diseases that gene therapy can treat."
- "But for cures for genetic disease not to change appearance or personality."
- "It seems much more positive than the media portrays."
- "Previously believed it was mainly concerned with the altering of a person's genetic make-up and germline therapy."
- "As a scientist I usually only see it with scientific interest. This session was very good because it enable me to see it from the perspective of affected people. Also because I feel that public education is very important otherwise it would be like the GM food issue."
- "Less advanced as regards applications to patients than I thought."

5.3 SPEAKERS' BIOGRAPHIES

Professor Norman C Nevin OBE BSc MD FFPH FRCPath FRCPEd FRCP, GTAC Chairman.

Norman C Nevin is Emeritus 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 GTAC and is currently Chairman. His research interests have resulted in over 300 peer reviewed publications on various aspects of genetics, especially single gene disorders and congenital abnormalities. In 2003, he received an OBE for his services to gene therapy.

Mr Michael Harrison, GTAC lay Member (Chair).

Michael Harrison is a practising Barrister in the field of clinical negligence and complex personal injury law. His primary interests relate to medical research, the ethical, legal and social implications of human genetic research and manipulation. He is an expert on the legal and ethical processes relating to biotechnology, especially gene therapy, and medical research. In addition to his training as a lawyer, Michael has been awarded a MA in Medical Law & Ethics from Kings College, London.

Michael has been a member of GTAC since 1998 and the Chair of the Local Research Ethics Committee for University College London Hospital NHS Trust. Recently, he advised about the lawfulness of the (then) proposed regulations under the 1990 HFEA, which would have permitted human cloning. Since then he has given further ethical and legal advice on submissions to House of Lords Select Committee on stem cell technology. In July 2001, Michael gave oral evidence in public as expert adviser on legal and ethical issues relating to stem cell technology & cloning before the House of Lords Select Committee.

Mrs Rosie Barnes, Chief Executive of the Cystic Fibrosis Trust.

Rosie Barnes is the Chief Executive of the Cystic Fibrosis Trust. She was a Member of Parliament (S.D.P) for Greenwich between 1987 and 1992. Prior to that she was involved in market research and marketing. She is a former member of GTAC.

Her interests in Parliament included health, education and the problems of children in care. She joined the Cystic Fibrosis Trust in 1996, after four years as Director of WellBeing, formerly Birthright. She takes a keen interest in the N.H.S, particularly in relation to the clinical care of those with Cystic Fibrosis. She is also very committed to the development of effective gene therapy for CF.

Mrs Fiona Sandford, GTAC lay Member and Vice President of the Primary Immunodeficiency Association.

Fiona Sandford is a lay member of GTAC and a Vice President of the Primary Immunodeficiency Association. She helped found the PiA in 1989, and chaired the Association from 1992–1996. She was also trustee of the Jeans for Genes campaign from its inception in 1994 until 2003. One of her children was born with a combined

immunodeficiency. He had a bone marrow transplant from his sister six years ago when he was nine, and is now fit and well.

Fiona's 'day job' is Director of Careers Services at the London School of Economics.

Dr Richard Ashcroft, GTAC lay Member and Senior Lecturer in Medical Ethics at Imperial College London.

Richard Ashcroft is Senior Lecturer in Medical Ethics at Imperial College London, where he heads the Medical Ethics Unit. He trained in mathematics and philosophy at Cambridge, where he obtained a PhD on ethics in science. He has a long standing interest in ethical and social issues in medical research, having published many articles in this area and having served as a member of NHS research ethics committees for a number of years. He is also a member of the ethics committee of the Royal College of Obstetricians and Gynaecologists.

Dr Geoff Watts, science writer and broadcaster

Geoff Watts read zoology at King's College, London, spent a year doing cancer research at St Mary's Hospital Medical School, and then moved to the Institute of Ophthalmology to work on lasers. Having completed a doctoral thesis he left research for scientific and medical journalism. For many years he was the deputy editor of World Medicine magazine. He went on to present BBC Radio 4's prize-winning Medicine Now throughout its 17 year life. He now presents the Radio 4 science programme Leading Edge, and divides his time between writing, broadcasting, and media consultancy work. He is a Fellow of the Academy of Medical Sciences and a member of the Government's Human Genetics Commission.

5.4 PRESENTATIONS

Professor Norman C Nevin OBE, GTAC Chairman

Reflections on 10 Years of UK Gene Therapy

The term "gene therapy" encompasses therapeutic procedures in which genes are intentionally introduced into human cells. There are two main approaches: *in vivo* gene therapy which is the direct introduction into target cells in the body, and *ex vivo* gene therapy in which the target cells are modified outside the patient and then re-implanted.

It is now 10 years since the first UK trial of gene therapy. Gene therapy was originally envisaged as a treatment for inherited disorders such as cystic fibrosis. Gene therapy can also be used to destroy unwanted cells such as cancer cells, and it is to this end that the majority of trials are currently directed. Gene therapies are also being developed to treat vascular and infectious diseases.

The Gene Therapy Advisory Committee (GTAC) oversees the conduct of gene therapy in the United Kingdom. GTAC considers and advises 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.

The presentation explored the past, present and future of gene therapy.

Mrs Rosie Barnes

Patients' Perspectives on Gene Therapy

Cystic fibrosis is the UK's most common life threatening inherited condition. Although both life expectancy and quality of life have improved markedly over the past 40 years, life for those with CF is still curtailed, with a current average life expectancy of 31 years. This is only achieved with a heavy burden of tedious and often uncomfortable daily treatment.

When the gene which causes cystic fibrosis, was identified in 1989, hopes of a cure for CF via gene therapy soared. As it became clear there was a great deal of work to be done to achieve this, especially to overcome the obstacles to delivery of the correct gene, disappointment set in and many scientists moved into other fields, not least because of the availability of funding for research into diseases which are far more common than CF.

The Cystic Fibrosis Trust recognises the importance of gene therapy for CF in terms of managing this condition in a far more effective way than has been possible to date. To enable it to become a clinical reality, a focussed, determined and realistic research programme was necessary. We therefore established the UK Gene Therapy Consortium, whereby the three teams in the UK who have been to the forefront of gene therapy for CF agreed to work as a team rather than as competitors, to facilitate progress and avoid duplication of effort. The cost of this initiative is a challenge for a Charity with a patient base of 7,500, but progress is encouraging.

Research is focusing on overcoming the barriers to effective delivery of the gene, identifying viable vectors and identifying the location and number of cells, which need to be accessed and corrected.

At present, we are trying to correct somatic cells, but in the fullness of time, we hope to be able to identify and correct the relevant stem cells.

The Cystic Fibrosis Trust sees gene therapy for CF as an effective treatment which would not only take the 'life threatening' out of the condition, it would also reduce the huge burden of daily care which becomes heavier as the disease progresses.

Improved treatment of the underlying problem by gene or drug therapy is now our top priority, whilst not ignoring other important research and family support.

Mrs Fiona Sandford

Parents' Perspectives on Child Gene Therapy

Gene therapy has been seen as the 'light at the end of the tunnel' for many families affected by a genetic disorder, however the past decade has been a roller coaster of raised hopes and disappointments as one gene therapy trial after another failed to live up to families' expectations.

This changed three years ago when doctors in Paris announced the success of a gene therapy trial on children suffering from Severe Combined Immunodeficiency. This success was repeated in the UK, and so far a total of 14 children have been successfully treated by gene therapy.

Two of the children in the Paris trial went on to develop a leukaemia-like illness. So what does gene therapy mean for the families of children who have a severe immunodeficiency? This presentation looked at what it's like to live with one of these conditions, what conventional treatments are available, at some family case students and what choices gene therapy offers these families.

Dr Richard Ashcroft

Ethics, Gene Therapy and an Uncertain World

Gene therapy has been surrounded by ethical debate, sometimes heated, for many years. Early debates (in the 1960s and 1970s) tended to concentrate on the idea that genetic modification of humans involved a fundamental transformation in human nature, and in our attitudes to humans. Subsequently, with the development of approaches to gene-based medicine which concentrated on correcting or alleviating the effects of single gene disorders, ethical debate concentrated on the risks and benefits of experimental therapies for the recipients. More or less consistent agreement has been achieved on a number of issues: the need to prohibit germline modification; the need to distinguish between therapies (which correct or treat disorders and diseases) and enhancements (which seek to improve the normal functioning of some trait); and the need to have very careful safety monitoring of experimental gene therapies during and after trials. The debates over gene therapy sometimes exaggerate the possibilities for genetic modification in humans, and many of the early debates now seem over-optimistic about what can be achieved with current technologies, and over-pessimistic about the implications of gene therapy for human dignity and integrity. A more realistic understanding of what gene therapy is today will help focus debate on matters closer at hand: appropriate regulation in a world context; allocation of resources and research effort; and the trade-off of risks and benefits to the seriously ill participants in research, and to future patients.

Dr Geoff Watts

Gene Therapy and the Media

Gene therapy has had a mixed but not unsympathetic treatment at the hands of the media – especially by comparison with the response to the advent of GM crops. This is probably because the benefits to the community of gene therapy are more obvious than those of GM technology – the most highly publicised examples of which seem to offer more to producers than consumers.

But gene therapy has had its setbacks. These are particularly damaging because a death associated with this still novel approach to disease often leads critics to question not only the application concerned, but gene therapy in general. This branch of experimental medicine could still suffer badly if the media choose to turn against it. An attempt to understand the disastrous media coverage of the GM debate serves as a lesson – and also a warning of what may happen if potentially controversial issues in gene therapy are mishandled.

The treatment of science by the media has attracted much academic research interest in recent years. One of the most illuminating studies was carried out at the Cardiff University School of Journalism. Its conclusions will be examined to see what bearing they have on the issue of gene therapy.

SECTION 6: GENE THERAPY COMMITMENTS IN THE GOVERNMENT'S WHITE PAPER

The following is an excerpt of the Government White paper "Our Inheritance, Our Future Realising the potential of genetics in the NHS", published in June 2003.

The full text can be found at:
http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/Genetics

GENE THERAPY RESEARCH

5.24 Gene therapy offers the potential to cure or alleviate inherited conditions by introducing new genes into the body to replace or augment faulty genes. Currently, most clinical trials into gene therapy aim to treat cancer. Although there have been some noted successes in treating single gene disorders with gene therapy, this type of gene therapy research is less attractive to industry because of the small numbers of patients with a given disorder. To address this, the Department of Health will invest up to £3 million to support gene therapy research into single gene disorders. Boosting research in this area now has the potential to benefit the estimated three-quarters of a million patients in this country with single gene disorders that are currently incurable.

5.25 Cystic fibrosis is the most common inheritable single gene disorder in this country. There are 7,500 children and young adults with cystic fibrosis in the UK. The primary symptom of this distressing condition is that mucus continually builds up in the lungs causing breathing difficulties and respiratory infections. Patients can also suffer gastro-intestinal and fertility problems. There is no cure for cystic fibrosis although regular physiotherapy, antibiotics and enzyme supplements can slow the progression of the disease. Current life expectancy for children born with cystic fibrosis is about 30 years. In addition to the funding set out above, the Department of Health will make available £2.5 million over 5 years to support gene therapy research for cystic fibrosis.

5.26 We will also take action to remove barriers to gene therapy clinical research for NHS and public sector researchers who do not have commercial sponsorship. One major difficulty is the cost of producing vectors, which have to deliver the new genetic material to the appropriate part of the body. These substantial costs will increase further once the new clinical trials directive becomes part of UK law in May 2004. The Clinical Trials Directive (2001/20/EC) requires higher standards for the manufacturing of materials for clinical trials, including gene therapy vectors.

5.27 In order to ensure that NHS researchers are not disadvantaged by these new requirements the Department of Health will invest up to £4 million to provide NHS and other public sector researchers with access to high standard gene therapy vector production facilities. This funding should be sufficient to meet the full need for gene therapy vectors within the NHS for both research and treatment over the next five years.

5.28 As with any branch of medicine it is not possible to know in advance of extensive clinical experience what the full range of potential side effects of gene therapy might

be. For example, some gene therapy treatments use a virus to deliver the therapeutic gene into chromosomes of the patient's cells. However the process is largely random and the virus could insert anywhere in the patient's genome, potentially leading to disruption of normal genes. The Department of Health will fund research into the long-term safety of the use of gene therapy vectors which are designed to insert into human genetic material. This research should be invaluable in minimising the risks and maximising the benefits of gene therapy.

PROGRESS

The commissioning process for the gene therapy commitments for single gene disorders, cystic fibrosis and long-term safety of gene therapy vectors is nearing completion. It is expected that the successful applications will be announced in Spring 2004.

SECTION 6: ANNEXES

ANNEX A: GLOSSARY

AAV

Adeno-associated virus.

Adenovirus/adenoviral

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

Adenocarcinoma

A cancer in cells that form the lining of the glands in the body, called adeno cells.

Angiogenesis

The growth of new capillary blood vessels into a tissue.

Antigen

Substances which are capable, under appropriate conditions, of inducing a specific immune response. Antigens may be soluble substances, such as toxins and foreign proteins, or particulates, such as bacteria and tissue cells.

Antibody

Produced by cells of the immune system called *B-cells*. Antibodies are proteins which lock onto antigens in a specific manner triggering a specific immune response against the antigen.

APC (antigen presenting cell)

A cell that carries on its surface *antigen* and presents the antigen to *T-cells*.

Artery

Blood vessel carrying blood away from the heart.

Atherosclerosis

The progressive narrowing and hardening of arteries over time.

B-Cell

A type of lymphocyte (white blood cell) normally involved in the production of antibodies to combat infection.

CABG (Coronary Artery Bypass Graft)

Pronounced "cabbage". An operation to bypass a blockage in the arteries supplying the muscle of the heart by taking a vein from the leg (or the mammary artery from the chest) and connecting it above and below the blockage.

Carcinoma

A malignant new growth that arises from epithelium, found in skin or, more commonly, the lining of body organs, for example: breast, prostate, lung, stomach or bowel.

CAT Scan (Computed Tomography)

A special radiographic technique that uses a computer to assimilate multiple X-ray images into a 2 dimensional cross-sectional image. This can reveal many soft tissue structures not shown by conventional radiography.

Cell

The smallest unit of living organisms which, given the right conditions, can survive independently and reproduce itself. It has been estimated that the body of a human adult comprises 50 million cells.

Cell Line

A cell line is a permanently established cell culture that will proliferate indefinitely given appropriate fresh medium and space.

Chemotherapy

Treatment with chemicals that destroy cancerous tissue.

Chromosomes

The self-replicating genetic structures of *cells* containing the cellular *DNA* which bears the gene sequence. Each human cell normally has 46 chromosomes. 44 chromosomes are 22 matching pairs, where one chromosome of each pair is inherited from each parent. The other two chromosomes are the X and Y sex chromosomes. Normally, females have XX and males have XY.

Clinical trial

Research study conducted with patients to evaluate a new treatment or drug.

CMV (cytomegalovirus)

Probably the most wide-spread of the herpes group of viruses.

CTL (cytotoxic T-lymphocyte)

A sub-set of white blood cell that is responsible for lysing target cells and for killing virus infected cells.

Cytokines

Messengers (hormone like substances) released by cells that have specific effects on cell-cell interaction, communication and the behaviour of other cells.

Cytogenetics

The study of the structure of *chromosomes* and cell division. Cytogenetic tests detect chromosomal abnormalities or abnormalities in the number of chromosomes.

Cytotoxicity

The property of being able to kill cells directly.

Dendritic Cell

Specialised cells of the immune system which can be found in skin.

DNA (deoxyribonucleic acid) (also "Genetic code")

The double stranded helical chemical molecule that encodes genetic information. It is the code for life. The genetic code of nearly all living things is made of DNA.

EBV (Epstein-Barr virus)

A Herpes virus which can cause glandular fever (as does CMV) and some cancers.

Enzyme

Enzymes are specialised *proteins* that are responsible for many functions in the body such as digesting food, and building bones and other tissue.

Epitope

The portion of an *antigen* that combines with its corresponding antibody.

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.

FGF (Fibroblast Growth Factor)

A *cytokine* which has been shown to stimulate blood vessel formation.

Ganciclovir

A drug which can be given to fight viral infections such as CMV and Herpes.

Gene

The fundamental physical and functional unit of heredity. A gene is a sequence of DNA that codes for one, or more, *protein*. A virus such as HIV has under a dozen genes, bacteria can have about 5,000 genes, yeasts can have about 7,500, and humans have around 30,000 genes.

Genetic condition, disease or disorder

Conditions which are direct consequences of defects in a single *gene* or in whole *chromosome*, parts of which may be lost, duplicated or misplaced; or due to the interaction of multiple genes and external factors. Later in life such interactions appear to be the basis of many of the common serious disorders, such as heart disease, diabetes and cancer.

Genome

A person's genome is their total genetic information i.e. everything contained in their DNA.

Germline cell

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

Glioblastoma

A type of brain tumour that arises from the specialised cells that surround neurons, providing mechanical and physical support and electrical insulation between neurons.

GMCSF (Granulocyte macrophage colony stimulating factor)

A *cytokine* produced by cells in response to inflammation or infection. GMCSF stimulates the growth and activation of white blood cells.

GVHD (Graft vs Host Disease)

A common and serious complication of bone marrow transplantation where there is a reaction of the donated bone marrow against a patient's own tissue.

HIV (Human Immunodeficiency Virus)

The agent responsible for Acquired Immuno Deficiency Syndrome (AIDS).

HPV (Human Papilloma Virus)

A sexually transmitted virus that causes warts. Thought to be related to the development of cancers of the cervix, vulva and anus.

HSV (Herpes simplex)

The virus responsible for causing cold-sores.

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 of strengthen the body's immune system.

Intracoronary Administration

Delivery of a drug into the arteries that supply the heart muscle.

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.

Intradermal

In the skin. An intradermal injection is given into the skin.

Intramuscular

Within the substance of a muscle. An intramuscular injection is given into the muscle.

Intraperitoneal

Within the cavity that contains the abdominal organs.

Intratumoural

Within a tumour. An intratumoural injection is given into a tumour.

In Utero

In the womb (uterus).

Ischaemia

A low oxygen state usually caused by obstruction of blood flow in tissue.

Lentivirus

Family of retroviruses of which HIV is a member.

Leukaemia

A disease characterised by abnormal increase in the number of white blood cells derived from a single lineage.

Lymphocytes

White blood cells that fight infection and disease.

Lymphoid

Pertaining to the lymphatic system, the tissues and organs (including the bone marrow, spleen, thymus and lymph nodes) that produce and store cells that fight infection and the network of vessels that carry lymph.

Malignant

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

Merkel Cells

Cells found in the skin. They are believed to have a function in the sense of touch.

Metastatic, metastases

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

MRI (Magnetic Resonance Imaging)

A special imaging technique (involving the use of a large magnet to polarise hydrogen atoms in the tissues) used to image internal structures of the body, particularly the soft tissues.

Mutagenesis

A process that leads to the development of genetic mutations (or changes).

Mutation

The change in a gene or chromosome that can cause a disorder or inherited susceptibility to a disorder.

MVA (Modified Vaccinia Ankara)

The vaccine strain of the pox virus which was used in the eradication of small pox.

Neoplasm

New and abnormal growth of tissue, which may be benign or cancerous.

NGF (Nerve Growth Factor)

A growth factor which attracts nerve cells, promotes their growth and which protects them from cells death.

Nucleus

A structure in the cell which contains the *chromosomes*.

Oncogene

A mutated and/or over-expressed version of a normal gene that can release the cell from normal restraints on growth and thus in concert with other changes, convert a cell into a tumour cell.

Pancreas

A body organ that is located in the abdominal cavity adjacent to the small intestine. It is responsible for the production of digestive fluids and *enzymes*. It also produces insulin.

PCR

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

PEG

A hydrophilic polymer (polyethylene glycol) that interacts with cell membranes.

Penetrance

The penetrance of a genetic mutation is the proportion of people with that mutation who develop that particular *genetic condition*. Penetrance is often expressed with reference to a particular age. For example, the penetrance of certain BRCA1 gene *mutations* (for breast/ovarian cancer) by age 70 has been estimated to be up to 85%.

Peptide

A small part of a *protein*. *Epitopes* are peptides.

Pharmacokinetics

The action of drugs in the body over a period of time, including the processes of absorption, distribution, localisation and excretion.

Phase I Clinical Trial

The earliest stage clinical trial for studying an experimental drug in humans. Phase I trials are generally comparatively small and are used to determine toxicity and maximum dose. The patients in these trials usually have advanced disease and have already received best available treatment.

Phase II Clinical Trial

Usually focus on the activity of the new product as a single agent in a non-comparative study.

Phase III Clinical Trial

An advanced stage clinical trial that should conclusively show how well a drug works as compared to other treatments. Phase III trials are large, frequently multi-institution tests. They generally compare the relative value of the new drug compared with the current standard treatment.

PIL

Patient Information Leaflet, also referred to as Patient Information Sheet.

Placebo

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

Placenta

Also called the afterbirth. The placenta is a specialised organ that supports the embryo and foetus during prenatal development. It contains approximately 150 ml of maternal blood.

Plasmid

A small piece of DNA that can be transferred from one organism to another.

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. Their genome consists of *RNA*. They are made inert so that they can enter a human cell carrying a gene for gene therapy without causing disease.

RNA (ribonucleic acid)

The molecule in the cell which transfers information from *DNA* to the *protein*-forming machinery of the cell.

Seroconversion

The change of a blood test from negative to positive, indicating the development of antibodies in response to infection or immunisation.

Somatic Cell

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

Stem Cell

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

T-Cell

A class of *lymphocytes* (white blood cells), so called because they are derived from the thymus.

Transcription

Synthesis of RNA in the cell using a DNA template.

Transduction

The process by which viruses transfer their genetic material to cells.

Translocation

Rearrangement of a chromosome in such that a part of the chromosome has been moved either within the same chromosome or to another chromosome.

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.

Umbilical blood

Is a source of haemopoietic stem cells (HSC). Contains stem cells within the umbilical cord.

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.

VEG-F (Vascular Endothelial Growth Factor)

A *cytokine* responsible for the growth of blood vessels.

Vector

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

Vein

A blood vessel that carries oxygen depleted blood to the heart.

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.

Wild-type

A strain (or virus, bacterium, plant or animal) found in nature or a standard strain.

X-Linked recessive disorders

Those disorders due to a mutation on the X chromosome. X-linked recessive disorders usually only affect males, but the disorders can be transmitted through healthy female carriers. Examples are haemophilia, X-SCID, and muscular dystrophy.

X-SCID

An inherited disorder affecting mainly boys in which the immune system fails to develop normally leaving the child susceptible to infections.

ANNEX B: GTAC ANNUAL REPORTS

Free copies of the annual reports and GTAC's publications can be downloaded from the GTAC website, see: http://www.advisorybodies.doh.gov.uk/genetics/gtac/publications.htm

[1] First Annual Report. January 1994-December 1994. Health Departments of the United Kingdom. London. Department of Health. 1995.

[2] Second Annual Report. January 1995-December 1995. Health Departments of the United Kingdom. London. Department of Health. 1996.

[3] Third Annual Report. January 1996-December 1996. Health Departments of the United Kingdom. London. Department of Health. 1997.

[4] Fourth Annual Report. January 1997-December 1997. Health Departments of the United Kingdom. London. Department of Health. 1998.

[5] Fifth Annual Report. January 1998-December 1998. Health Departments of the United Kingdom. London. Department of Health. 1999.

[6] Sixth Annual Report. January 1999-December 1999. Health Departments of the United Kingdom. London. Department of Health. 2000.

[7] Seventh Annual Report. January 2000-December 2000. Health Departments of the United Kingdom. London. Department of Health. 2001.

[8] Eighth Annual Report. January 2001-December 2001. Health Departments of the United Kingdom. London. Department of Health. 2003.

[9] Ninth Annual Report. January 2002-December 2002. Health Departments of the United Kingdom. London. Department of Health. 2003.

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 and Healthcare products Regulatory Agency (MHRA) (formerly: the Medicines Control Agency MCA), the Health and Safety Executive, and the Department for Environment Food and Rural Affairs (DEFRA);

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

The Committee has a responsibility for:

(a) Providing advice for applicants on:

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

  (ii) The design and conduct of the research;

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

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

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

  (i) The clinical status of the subjects;

  (ii) The scientific quality of the proposal;

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

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

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

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

ANNEX D: MEMBERSHIP OF GTAC

GTAC Members

- Professor Norman Nevin (Chairman),
  Emeritus Professor of Medical Genetics, Queen's University, Belfast.
- Dr Richard Ashcroft (new member from August 2003),
  Medical Ethicist, Imperial College London
- Mrs Deborah Beirne,
  Senior Research Nurse, St. James Hospital, Leeds
- Dr Caroline Benjamin,
  Macmillan Genetic Counsellor, Liverpool Women's Hospital NHS Trust
- Mr David Crosby (until May 2003)
  Retired Surgeon, Cardiff
- Professor Martin Gore,
  Consultant Clinical Oncologist, The Royal Marsden Hospital, London
- Professor Terence Hamblin,
  Consultant Haematologist, University of Southampton and Royal Bournemouth Hospital
- Dr Peter Harris,
  Technical Director, KuDOS Pharmaceuticals Ltd.
- Professor David Harrison,
  Professor of Pathology and Medical Researcher, Department of Pathology, Edinburgh University
- Mr Michael Harrison,
  Barrister, London
- Professor Nicholas Lemoine,
  Professor of Molecular Pathology, Cancer Research UK Molecular Oncology Unit, Hammersmith Hospital, London
- Dr Adrian Lepper (new member from August 2003)
  Chartered engineer, Hertfordshire
- Professor Andrew Lever,
  Professor of Infectious Diseases, University of Cambridge
- Professor Alex Markham,
  Professor of Molecular Medicine, University of Leeds

- Professor James Neil
  Professor of Virology and Molecular Oncology, University of Glasgow

- Reverend Dr Lee Rayfield
  Vicar and former Immunologist, Berkshire

- Mrs Fiona Sandford
  Patient Advocate, Hertfordshire

- Dr Michael Waterhouse,
  Television Producer and Author, Southborough

Observers

Department of Health:

- Ms Elizabeth Woodeson

Medicines and Healthcare products Regulatory Agency (MHRA):

- Dr Philip Harrison

Health and Safety Executive:

- Dr Michael Mackett

Secretariat (Department of Health)

- Dr Monika Preuss (new Secretary from April 2003)
- Dr Jayne Spink
- Ing. Daniel Gooch (acting Secretary, January to March 2003)
- Mrs Margaret Straughan

ANNEX E: REGISTER OF MEMBERS INTERESTS

GTAC Member	Declared interests
Professor Norman Nevin	None
Professor Nick Lemoine	• Research Unit supported by UK charities and commercial bodies. • Director of Gene Expression Technologies • Consultant on EntreMed, Gendux & IC-Vec
Ms Caroline Benjamin	Husband employed as Finance Manager for ConvaTec, Bristol Myers Squib, UK
Mr David Crosby	None
Professor Martin Gore	• Ad hoc consultancy to Schering-Plough, Bristol Myers Squib, Aventis, Novartis, Pierre Fabre, Debiopharm, and Chiron. • Consultant, Cambridge Antibody Technology
Professor Terence Hamblin	Ad hoc consultant to and research funds from Schering AG, Roche and Celgene.
Mr Michael Harrison	• Managing director of Bioethics Consulting Ltd. • Independent practising barrister working in the field, interests are declared as appropriate
Professor David Harrison	• Consultancy & Shareholding – Medical Solutions plc • Shares – The Forensic Institute • Collaborative research – AstraZeneca, Etiologics Ltd • Directorship – EMMS (International) and EMMS (Nazareth) – both registered charities
Professor Andrew Lever	Consultancy & Shareholding in SynGenix Ltd
Professor Alex Markham	• Scientific Advisory Board Member of Oxagen Ltd. • Chief Executive Officer, Cancer Research UK • Director: Bioscience Venture Capital Trust
Professor James Neil	None

Mrs Deborah Beirne	Work involves gene therapy trials
Dr Peter Harris	Consultant to ML Laboratories Plc.
Dr Adrian Lepper	• Secretary to the Board eLearning Holding company • Member of Corporation and Governor West Herts College • Independent consultancy assignments • Wife has a small shareholding in Glaxo Smith Kline.
Dr Richard Ashcroft	None
Revd Dr Lee Rayfield	None
Ms Fiona Sandford	Shares in Australian Mutual Provident
Dr Michael Waterhouse	None

ANNEX F: EXTERNAL EXPERT ADVISERS TO GTAC

GTAC is extremely grateful to all its expert advisers for their support in the review of applications and for their input of expertise and advice in 2003. The following expert advisers have agreed to be named in this report:

- Professor Jon Austyn, Oxford University
- Dr Angela Bowman, Western General Hospital, Edinburgh
- Dr Stacey Efstathiou, Cambridge University
- Professor Finbarr Cotter, Barts and The London School of Medicine
- Professor J George Dickson, Royal Holloway, London
- Professor Farzin Farzaneh, The Rayne Institute
- Dr Thomas Friedberg, University of Dundee
- Professor Ian Hart, St Thomas' Hospital, London
- Professor Robert Hawkins, Christie Hospital, Manchester
- Dr Sarah Howie, Edinburgh University
- Professor Patrick Johnson, Belfast City Hospital
- Dr Douglas Lowrie, National Institute for Medical Research, London
- Professor Maxine Partridge, King's College, London
- Professor Jonathan Weber, Imperial College London

ANNEX G: SUMMARY OF UK GENE THERAPY TRIALS 1993–2003

AN ANALYSIS OF 10 YEARS OF UK CLINICAL GENE THERAPY

Since 1993, when the first gene therapy study was conducted in the UK, GTAC processed 98 applications in total. Of these, 90 applications were approved (or conditionally approved), four approved trials were subsequently withdrawn (including one in 2003), and one full application is outstanding. The remaining 85 gene therapy trials, open and closed, are analysed below.

In these 85 trials, 711 patients were enrolled by December 2003, approximately 75% in cancer trials. The following 3 figures analyse the studies in terms of the year in which they were approved (Figure 1), the vector system used to deliver the therapeutic genes (Figure 2), and the disease (Figure 3). As shown in Figure 3, almost three quarters of all approved UK gene therapy trials, 61 in total, are for the treatment of cancers. Figure 4 breaks down this data in more detail.

Figure 1: GTAC approved trials (open and closed) by year (n = 85).

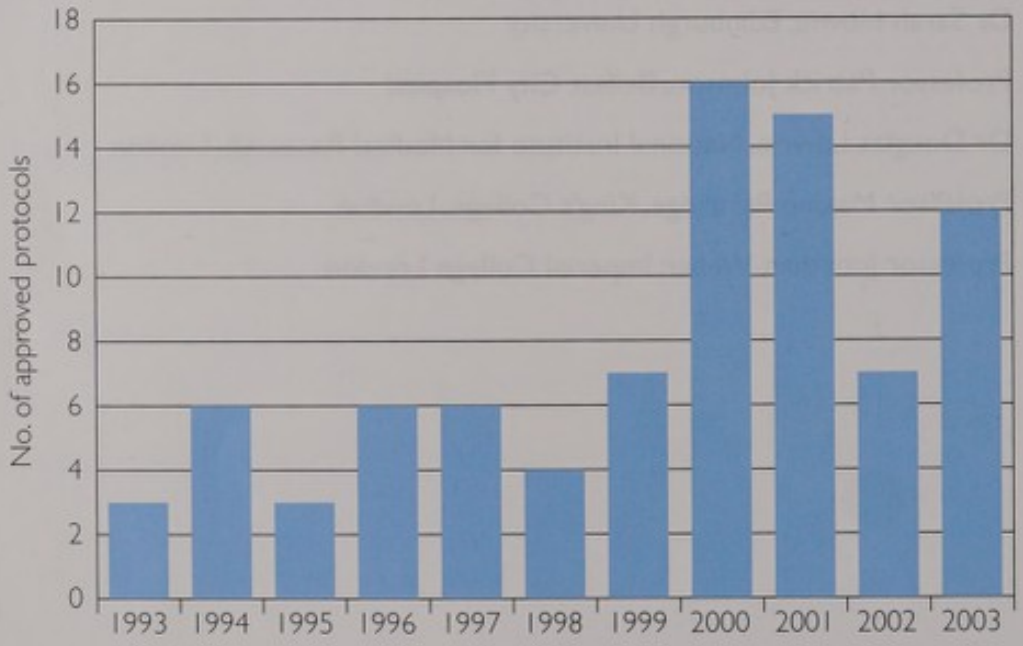


Figure 2: **GTAC approved trials by vector system (n = 85). Other: antisense or canary pox.**

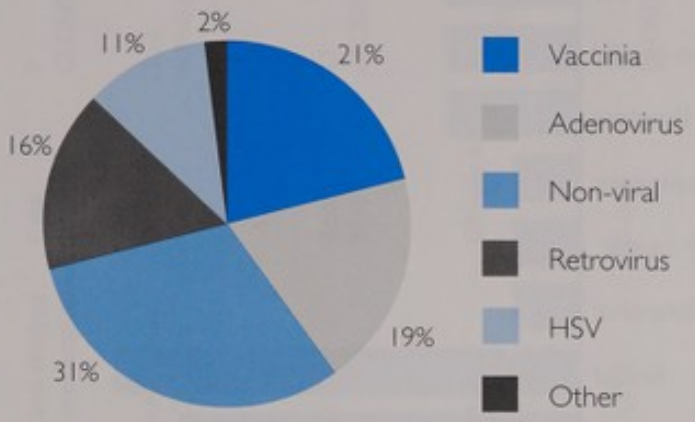


Figure 3: **GTAC approved trials by disease (n = 85).**

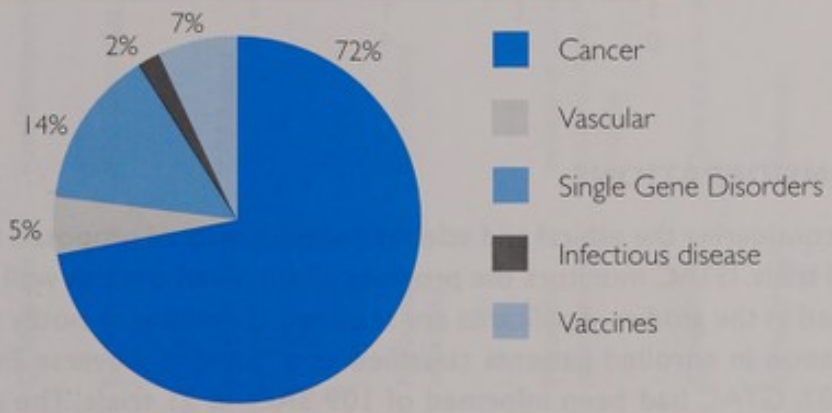
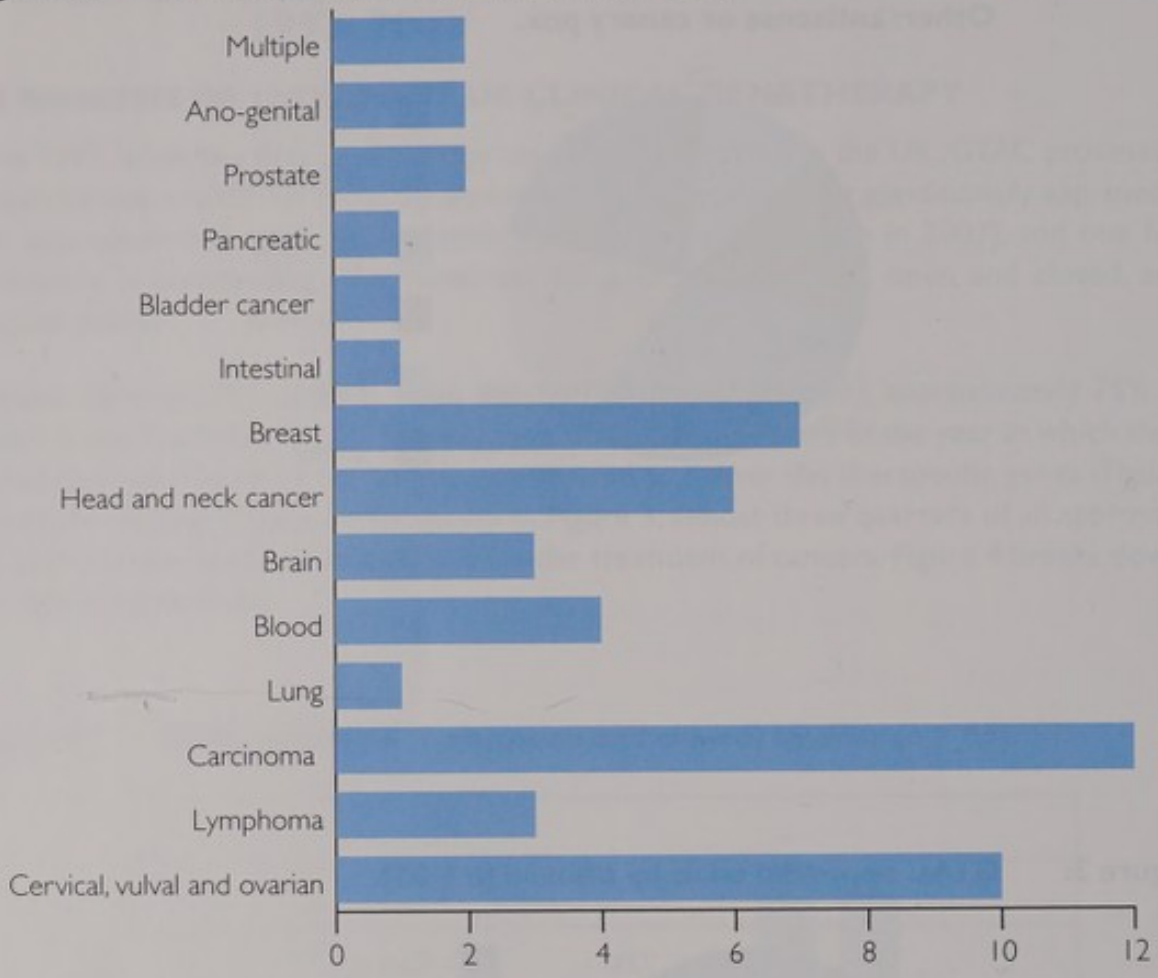


Figure 4: GTAC approved cancer trials (n = 61).



SAFETY CONSIDERATIONS

In addition to considering the ethical and scientific acceptability of proposals for human gene therapy clinical trials, GTAC monitors the progress of approved trials as well as the safety of patients enrolled in the studies. Applicants are required, therefore, to notify the Committee of any observation in enrolled patients classified as a "Serious Adverse Event" (SAE). By December 2003, GTAC had been informed of 109 SAEs in 21 trials. The ongoing review of SAEs, and follow-up if necessary, is an important part of the Committee's business.

LATEST UK GENE THERAPY RESEARCH 1993–2003 (JANUARY 2004)

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

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

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

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

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
22	A multiple ascending dose study evaluating the safety and the gene transduction into malignant cells after the administration of EIA-lipd complex by intra-peritoneal administration in patients with epithelial ovarian cancer who over express HER–2/neu.	Ovarian Cancer	The John Radcliffe Hospital, Oxford; Guy's and St Thomas's Cancer Centre, London; Royal Marsden Hospital, London; St George's Medical School, London.	9–97	Plasmid	E1A HER2/ neu	*E. coli* STBL2	22 CLOSED
23	A pilot study of recombinant CEA vaccinia virus vaccine with post vaccination CEA peptide challenge in combination with 5-fluorouracil and folinic acid in the treatment of colorectal cancer (Phase I subcutaneous).	Colorectal Cancer	Queen Elizabeth Hospital, Birmingham	3–98	Vaccinia	CEA	CV1	Trial not yet open
24	A phase I study of intraperitoneal administration of a replication deficient adenovirus carrying a nitroreductase gene in ovarian cancer patients.	Ovarian Cancer	City Hospital NHS Trust and University Hospital NHS Trust Birmingham	3–98	Adenovirus	Nitroreductase	HEK–293	0 CLOSED
25	A multiple ascending dose study evaluating the safety and gene transduction into malignant cells after administration of E1A-lipid complex by intratumoral injection with unresectable or metastatic head and neck tumours.	Head and Neck	Royal London Hospital; Charing Cross Hospital	Submission withdrawn	Plasmid	E1A	HEK293	Submission withdrawn
26	A study of dose requirements, safety and local efficacy of intratumoral injection of the genetically modified non-virulent herpes simplex virus HSV ICP 34.5 negative mutant 1716 into accessible soft tissue nodules of secondary malignant melanoma.	Malignant Melanoma	Glasgow Western Infirmary and Southern General Hospital, Glasgow	9–98	HSV	ICP34.5 deleted	BHK–21/C13	5 CLOSED

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
27	The use of MetXia-P450 for the treatment of advanced breast cancer (Phase I/II intratumoral).	Breast Cancer	The Churchill Oxford	10–98	Retrovirus	Cytochrome P450	TEFLY-A	12 CLOSED
28	A phase I/II study of hepatic artery infusion with WTP53-CMV-AD in primary metastatic malignant liver tumours.	Liver Cancer	Hammersmith Hospital, London	Application Withdrawn	Adenovirus	p53	HEK293	Application withdrawn
29A	A Phase I/II pilot study of idiotypic vaccination for follicular B-cell lymphoma using a genetic approach	B-cell lymphoma	Royal Bournemouth Hospital; Southampton General Hospital; Christie Hospital Manchester	5–99	Plasmid	Idiotypic DNA vaccination	*E. coli* JM109	25 of 25–40
29B	A pilot study of donor idiotypic vaccination for the purpose of targeted post-transplant immunotherapy following allogenic bone marrow transplantation for multiple myeloma "EDLI"	Multiple myeloma	Southampton General Hospital; Nottingham City Hospital; University College London	5–00	Plasmid	Idiotypic DNA vaccination	*E. coli* JM109	2 of 15
29C	Phase I/II study of idiotypic vaccination for multiple myeloma using a genetic approach (MMIFTT)	Multiple myeloma	Royal Bournemouth Hospital; Southampton General Hospital	4–00	Plasmid	Idiotypic DNA vaccination	*E. coli* JM109	1 of 15
29D	Phase I/II study of idiotypic vaccination for chronic lymphocytic leukaemia using a genetic approach (CLLIFTT)	Chronic lymphocytic leukaemia	Royal Bournemouth Hospital; Southampton General Hospital	4–00	Plasmid	Idiotypic DNA vaccination	*E. coli* JM109	2 of 10 CLOSED
30	Use of a retrovirus carrying human cytochrome p450 for the treatment of ovarian cancer (Phase I intra-abdominal).	Ovarian Cancer	Northern General Hospital, Sheffield	2–00	Retrovirus	Cytochrome P450	TEFLY-A	6 CLOSED

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

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

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
45	Phase I clinical gene therapy protocol for X-SCID	X-SCID	Institute of Child Health, London	01–01	Retrovirus	Common gamma chain	PG13	5 of 20
46	Phase I gene therapy protocol for X-CGD	X-CGD	Institute of Child Health, London	12–00	Retrovirus	Gp91-phox	HEK293	1 of 5
47	A phase I, Randomised, Double-blind, Placebo Controlled, Escalating Dose, Multicentre Study of Ad2/Hypoxia Inducible Factor Gene Transfer Administered by Intramyocardial Injection During Coronary Artery Bypass Grafting Surgery in Patients with Incomplete Revascularisation	Coronary artery disease	John Radcliffe Hospital, Oxford	12–00	Adenovirus	HIF–1a/VP16	HEK293	0 of 4
48	A randomised phase I trial of intravenous CI–1042 with or without entanercept in patients with metastatic carcinoma	Metastatic carcinoma	Hammersmith Hospital, London	12–00	Adenovirus	p53	HEK293	Application withdrawn
49	A phase I/II Study of Immunotherapy for Patients with Metastatic Melanoma Using Dendritic Cells Transfected with a Plasmid Encoding Two Melanoma Antigens	Metastatic Melanoma	CRC Institute for Cancer Studies, Birmingham	02–01	Plasmid complexed with peptide	MART–1 gp–100	*E. coli*	0 of 10 Trial not yet open
50	A Phase II Trial of Preoperative intratumoural Injection with HSV1716 in Patients with Resectable Squamous Cell Tumours of the Head and Neck	Head and Neck Cancer	Southern General Hospital, Glasgow	05–01	HSV	ICP34.5 deleted	BHK–21/C13	20 of 20 CLOSED

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
51	A multinational multicenter, randomised, double-blind, placebo controlled study to evaluate the efficacy and safety of Ad5FGF–4 in patients with stable angina	Coronary Artery Disease	Papworth Hospital NHS Trust; Royal Sussex County Hospital; Royal Infirmary of Edinburgh; Hammersmith Hospital, London; King's College Hospital, London; Royal Free Hospital, London; St Thomas' Hospital, London; The London Chest Hospital; Wythenshawe Hospital, Manchester; Nottingham City Hospital; University Hospital Wales, Cardiff; Queen Elizabeth Hospital, Birmingham (to be confirmed)	05–01	Adenovirus	FGF–4	HEK293	15 of 60 in UK 67 of 450 world-wide *NOTE:* the trial was put on halt in January 2004. No further information was available at the time of print.
52	A phase I study to evaluate the safety, tolerability and immunogenicity of two administrations of either plasmid DNA (pSG.HBs) versus placebo or modified vaccinia virus Ankara (MVA.HBs) versus placebo, followed by two boost administrations of MVA.HBs expressing hepatitis B surface antigen in healthy male volunteers	Hepatitis B Vaccine Trial	TNO BIBRA International, Surrey; University of Oxford; Central Middlesex Hospital	08–01	Vaccinia and plasmid	HBsAg	MVA: Chicken embryo fibroblasts; Plasmid in *E. coli*	18 of 18 CLOSED
53	A pilot study of the safety and immunogenicity of a candidate HIV–1 clade A DNA vaccine, pTHr.HIVA, given by needle injection into the deltoid muscle in HIV–1-seropositive subjects receiving highly active anti-retroviral therapy	AIDS	John Radcliffe Hospital, Oxford	05–01	Plasmid	HIV–1 clade A *gag* and 25 HIV–1 *gag*, *pol*, *env*, *nef* CTL epitopes	1DH1	10 of 10 CLOSED

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
54	A Phase II, Randomised, double-blind, Placebo-controlled, Parallel Group, Efficacy and Safety Study of NV1FGF in Patients with Severe Peripheral Artery Occlusive Disease	Peripheral Artery Occlusive Disease	St. George's Hospital, London; Royal Bournemouth Hospital; Leicester Royal Infirmary; Wythenshawe Hospital, Manchester; Freeman Hospital, Newcastle; Royal Free Hospital, London (CLOSED); Bristol Royal Infirmary (CLOSED); Leeds General Infirmary (CLOSED); Southampton General Hospital (CLOSED)	08–01	Plasmid	FGF–1	1XAC–1	7 of 40
55	Gene directed enzyme prodrug therapy for the treatment of prostate cancer (Phase I intratumoral)	Prostate Cancer	Queen Elizabeth Hospital, Birmingham; Freeman Hospital Newcastle	04–01	Adenovirus	Nitro reductase	PER-C6	16 of 30
56	A Phase II, Multicentre, double-blinded, Placebo-Controlled, Dose-Finding Study of ZYC101a in the Treatment of high-grade Squamous Intra-Epithelial Lesions of the Uterine Cervix.	Ano-genital Neoplasia III	Hammersmith Hospital, London	11–01	Plasmid	HPV E6 & E7	*E. coli*	0 of 5 CLOSED
57	A Phase I, Multidose Study to Evaluate the Safety of Intramuscular Injections of HER–2 DNA in Patients with Metastatic Breast Cancer.	Breast Cancer	Hammersmith Hospital, London	11–01	Plasmid	HER–2	*E. coli*	27 of 27 CLOSED
58	The Use of a cDNA Vaccine Encoding the Human MUC1 Gene in the Treatment of Patients with Advanced Breast Cancer – A Phase I/II Study	Breast Cancer	ICRF, Guy's Hospital, London	08–01	Plasmid	MUC–1	*E. coli*	1 of 12–28

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
59	A phase IIa, open label trial to assess the safety, immunogenicity and efficacy of a prime-boost strategy of TA-CIN administered in associated with TA-HPV to patients with high grade ano-genital intraepithelial neoplasia (AGIN)	Cervical Cancer	University of Wales, Cardiff; St. Mary's Manchester; Addenbrooke's, Cambridge.	07–01	Vaccinia	E6 & E7 HPV	MR–5	29 CLOSED
60	Study of Transfection Efficacy and Safety of MetXia-OB83 in patients with cutaneous lesions of breast cancer or melanoma	Breast Cancer	Churchill Hospital, Oxford; Queen Elizabeth Hospital, Birmingham	07–01	Retrovirus	P450	TEFLYRD	7 of 8
61	An upward titration study of transfection efficacy and safety of Metxia-OB83 in patients with adenocarcinoma of the prostate	Prostate Cancer	The Churchill Hospital, Oxford.	08–01	Retrovirus	P450	TEFLYRD	CLOSED
62	First Administration to Man of an Oncolytic Herpesvirus Vector Containing a Transgene for Granulocyte Macrophage Colony Stimulating Factor (OncoVex^{GM-CSF}) – A Study of its Safety, Biodistribution and Biological Activity.	Melanoma, Breast, Head & Neck, cancer, Non-Hodgkins Lymphoma	Hammersmith Hospital, London; St George's Hospital, London; CR-UK Institute for Cancer Studies, University of Birmingham	11–01	HSV	ICP34.5-deleted ICP47-deleted Human GM-CSF	BHK 21c13	16 of 22
63	VTP–1/01: A Phase I/II Trial of Intravenous vs. Hepatic Arterial Infusion of an E1A-CR2 Deleted Adenovirus (VTP–1) in Patients with Inoperable, Metastatic Colorectal Carcinoma.	Metastatic colorectal carcinoma	Hammersmith Hospital, London	Application withdrawn	E1A conserved region 2 deleted & E3B RID gene region deleted	N/a	HEK–293	Application withdrawn
64	A Phase I trial of replication-competent herpes simplex virus (ICP 34.5 null mutant 1716) in patients with inoperable malignant pleural mesothelioma.	Malignant pleural mesothelioma	University of Glasgow, Beatson Oncology Centre, Glasgow	02–02	HSV HSV1716	ICP34.5 deleted	BHK–21/C13	0 of 9 Trial not yet started

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
65	A Phase I trial of PolyMEL, a polyepitope DNA vaccine in the treatment of metastatic melanoma patients.	Melanoma	St James Hospital, Leeds	01–02	Plasmid DNA (polyMEL)	Multiple melanoma epitopes	*E. coli*	1 of 12
66	A recombinant vaccinia Ankara (MVA)-based vaccine encoding Epstein-Barr Virus target antigens: phase I dose escalation trial to determine immunogenicity and toxicity in patients with EBV+ malignancy	Naso-Pharyngeal carcinoma	Institute of Cancer Studies, Birmingham	02–02	DNA plus MVA	EBV epitopes (EBNA1 and LMP2A)	CEF	0 of 12–15 Trial not yet open
67	Percutaneous Intramyocardial Gene Therapy against myocardial ischaemia with phVEGF-A165SR – A double-blind placebo controlled study	Coronary Artery Disease	Wythenshawe Hospital, Manchester	Application withdrawn	Plasmid	VEGF	*E. coli*	Application withdrawn
68	A Phase I trial of polyHER2neu – a polyepitope DNA vaccine encoding HER–2 epitopes in the treatment of breast cancer.	Breast Cancer	St James Hospital, Leeds	01–02	Plasmid DNA	Poly epitopes of HER–2	*E. coli*	0 of 12 Trial not yet open
69	A phase I/II study of vaccination with a DNA fusion gene containing an epitope of CMV in allograft donors and patients awaiting renal transplantation	CMV infection following transplant	Southampton General Hospital; Royal Free Hospital London; University College London Hospital	02–02	Plasmid DNA (pcDNA3)	Peptide from pp65 from CMV	*E. coli*	2 of 15 pairs
70	NUMBER NOT ALLOCATED							

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
71	A Phase I/II prospective study of immunogene therapy with a liposomally encapsulated replication incompetent Semliki Forest Virus (SFV) vector carrying the human interleukin–12 gene and administered intratumorally in patients with recurrent or progressing glioblastoma multiforme.	Glioma	University of Liverpool	Application withdrawn	Replication disabled Semliki Forest Virus, liposome encapsulated	Human IL–2	Baby hamster kidney (BHK)	Trial withdrawn
72	Phase I/II study to determine the optimum dose and dosing regimen then to assess the efficacy of a poly-epitope pharmaccine, involving pSG2.Mel3 and MVA.Mel3, in patients with Stage III or Stage IV metastatic melanoma	Metastatic melanoma	Christie Hospital, Manchester; Churchill Hospital Oxford' Western General, Edinburgh; Southampton General Hospital	09–02	DNA and MVA	Multiple melanoma epitopes	CEF	11 of 30–40
73	Phase I clinical gene therapy protocol for adenosine deaminase deficiency	Severe Combined Immunodeficiency	Great Ormond Street Hospital, London	12–02	Retrovirus (spleen focus forming virus)	Adenosine Deaminase	PG13	1 of 5
74	A randomised phase II trial of replication-competent herpes simplex virus (ICP 34.5 null mutant) HSV1716 in recurrent glioblastoma	Glioblastoma	Beatson Oncology Centre, Glasgow	Application pending	HSV	ICP34.5 deleted	BHK 21/C13	To be confirmed
75	A Phase I study of NYVAC C in healthy volunteers at low risk of HIV infection (EV01)	HIV–1	Imperial College London	02–03	MVA	HIV–1 Clade C *gag, pol, nef, env,* (NYVAC C)	Chick Embryo Fibroblasts	12 of 12 CLOSED
76	A phase I/II study of DNA vaccination with a CEA/pDOM fusion gene in patients with carcinoma expressing CEA	Carcinoma	Southampton General Hospital	02–03	Plasmid DNA (pcDNA3)	CAP–1 peptide from CEA	*E.coli*	0 of 30 Trial not yet open

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
77	Gene therapy protocol for the evaluation of the safety and efficacy of TroVax in conjunction with chemotherapy in patients with metastatic colorectal cancer	Metastatic colorectal cancer	Christie Hospital Manchester; Queen Elizabeth Hospital, Birmingham	02–03	MVA	Human Oncofoetal Antigen 5T4	Chick Embryo Fibroblasts	8 of 15
78	A phase I clinical gene therapy trial for X-SCID using umbilical cord blood	X-SCID	Institute of Child Health, London	02–03	Retrovirus (Moloney murine leukaemia virus)	Common gamma chain	PG13	0 of 10
79	A pilot study to evaluate the safety, tolerability and immunogenicity of a candidate HIV–1 vaccine, MVA.HIVA delivered to HIV–1 sero-positive adults receiving HAART	HIV–1	MRC Human Immunology Unit, John Radcliffe Hospital, Oxford	07–03	MVA	HIV–1 clade A *gag*, *pol*, *nef* and *env*	CEF	2 of 10
80	Phase I/II study – first administration of Dendritic cells transduced with ImmunoVEX$^{TRI\text{-}Melan}$ to patients with metastatic or inoperable melanoma	metastatic or inoperable melanoma	St George's Hospital Medical School, London	Application declined	HSV	Tyrosinase, hMART1, hGP100	*Vero (MEVP16/M4 F6A)*	Application declined
81	An open label study of TroVax given in conjunction with 5-Fluorouracil/ Leukovorin/Oxaliplatin: safety and immunogenicity before, during and after chemotherapy (TV2)	Colorectal cancer	University of Leeds School of Medicine; Hammersmith Hospital, London	05–03	MVA	Human oncofoetal antigen 5T4	CEF	1 of 15
82	A phase II trial to evaluate efficacy and safety of intramuscular injections of HER–2 DNA Autovac™ in patients with metastatic or locally advanced breast cancer	Breast cancer	Hammersmith Hospital	07–03	Plasmid	HER–2 with T cell epitopes P2 and P30 derived from tetanus toxin	*E. coli*	Trial withdrawn

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
83	A Phase I/II safety study of MetXia-OB83 in patients with pancreatic cancer	Pancreatic cancer	Royal Liverpool University Hospital, Leicester Royal Infirmary	10–03	Retrovirus (Moloney murine leukaemia virus)	cytochrome P450	FLY RD83	0 of 15 Trial not yet open
84	A Phase I study of immunotherapy for patients with metastatic melanoma using dendritic cells transfected with a plasmid encoding two melanoma antigens	Malignant melanoma	CRUK, Birmingham	07–03	Plasmid DNA	MART–1 and gp–100	*E. coli*	1 of 10
85	A phase I trial to assess the safety of DNA C, and the safety and immunogenicity of DNA C followed by NYVAC C in an open, randomised comparison to NYVAC C alone in healthy volunteers at low risk of HIV infection (EV02)	HIV–1	Imperial College London, St Mary's Hospital	10–03	Plasmid pORT1	HIV–1 clade C *gag, pol, nef, env*	*E. coli*	0 of 20 Trial not yet open
86	First administration of dendritic cells transduced with ImmunoVEX$^{\text{Tri-Melan}}$ to patients with metastatic or inoperable melanoma, preliminary assessment of safety, biodistribution and indicators of efficacy	Metastatic or inoperable melanoma	St George's Hospital Medical School, Southampton General Hospital	10–03	HSV	hTyrosinase, hMART1, hGP100	Vero (MEVP16/M4 F6A)	0 of 60 Enrolment not yet started.
87	A Phase II Study Immunologically Evaluating 5T4-MVA (TroVax) in Patients undergoing Surgical Resection of Colorectal Liver Metastases	Metastatic colorectal cancer	Christie Research Centre, Manchester	01–04	MVA	Human Oncofoetal Antigen 5T4	Chick Embryo Fibroblasts	0 of 20 Enrolment not yet started.
88	A Cancer Research UK Phase I Trial of AEG35156/GEM640 (XIAP antisense) administered as a 7 day continuous intravenous infusion in patients with advanced tumours	Advanced tumours	Christie Hospital NHS Trust, Edinburgh Royal Infirmary	12–03	N/a	Antisense DNA to human X-linked inhibitor of apoptosis	*N/a*	0 of 18–40 Enrolment not yet started.

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The GTAC Secretariat may be contacted at:

Department of Health
625C Skipton House
80 London Road
London SE1 6LH

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