
**GENE THERAPY
ADVISORY COMMITTEE**

ELEVENTH ANNUAL REPORT

**Covering the period from
January 2004 to December 2004**

**GENE THERAPY
ADVISORY COMMITTEE**

ELEVENTH ANNUAL REPORT

January 2004 to December 2004

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/>

CONTENTS

	PAGE
FOREWORD	
SUMMARY	
Section I: PROTOCOLS REVIEWED BY GTAC IN 2004	
I.1 Cancer	1
I.1.1 Prostate cancer	1
GTAC 089: A Phase I/II Trial of a DNA vaccine with a PSMA27/ pDom fusion gene given by intramuscular injection in HLA A2+ patients with prostate carcinoma with or without electroporation	2
I.1.2 Brain cancer	2
GTAC 090: A controlled, randomised, parallel group, multicentre study of the efficacy and safety of herpes simplex virus-thymidine kinase gene therapy (Cerepro™), with subsequent ganciclovir, for the treatment of patients with operable high grade glioma	3
GTAC 074: A randomised efficacy trial of herpes simplex virus HSV1716 in recurrent glioblastoma multiforme	3
I.1.3 Colorectal cancer	3
GTAC 092: A 2 x 2 factorial randomised phase II trial assessing anti-CEA, anti-MUC-I vaccination +/- chemotherapy +/- GM-CSF after surgery in patients with stage II colorectal cancer	3
GTAC 095: Safety and immunology evaluation of TroVax produced by the Baxter synthetic route in patients with stage IV colorectal cancer	4
I.1.4 Breast cancer	4
GTAC 094: A Phase II exploratory study of the efficacy and safety of OncoVEX GM-CSF in combination with Arimidex in the neoadjuvant treatment of breast cancer in post menopausal women with oestrogen receptor positive tumours	5
I.1.5 Blood cancer (leukaemia)	5
GTAC 098: A pilot study of lentivirus transduced acute myeloid leukaemia (AML) blasts expressing B7.1 (CD80) and IL-2, for the induction of graft versus leukaemia (GVL) effect in poor prognosis, relapsed AML	5

1.1.6	Multiple cancers	6
	GTAC 096: A phase I study of adoptive transfer of autologous tumour antigen-specific T cells with pre-conditioning chemotherapy and intravenous IL2 in patients with advanced CEA positive tumours	6
1.2	Cardiovascular disease	6
1.2.1	Coronary artery disease	6
	GTAC 097: A multicenter, randomised, double-blind, placebo-controlled study evaluating the efficacy of BIOBYPASS (ADGVVEGF121.10NH) delivered by NOGA™ -Guided/myostar catheter in no option patients with class II-IV stable angina	7
1.2.2	Peripheral artery disease	7
	GTAC 091: Double-blind, randomised, placebo-controlled, parallel group and dose-finding, multicentric, safety and efficacy study with intramuscular injections of NVIFGF in subjects with intermittent claudication	8
	GTAC 099: A phase 2, randomized, double-blind, placebo controlled, parallel-group, multicenter, dose-selection study of Ad2/hypoxia inducible factor HIF-1 α /VP16 in patients with intermittent claudication	8
1.3	Human immunodeficiency virus (HIV) infection	8
	GTAC 093: An open, randomised, parallel group study to evaluate the safety, tolerability and immunogenicity of the GW825780 DNA immunotherapeutic when delivered using the Powderject ND5.5 device to healthy adult volunteer subjects	9
Section 2:	AMENDMENTS TO ONGOING PROTOCOLS	10
Section 3:	GUIDANCE ISSUES	16
3.1	Advice to researchers	16
3.2	Horizon scanning activities	16
3.3	Lentiviral safety	18
Section 4:	REGULATORY ISSUES	20
4.1	Workshop on antisense technologies and review of GTAC’s definition of gene therapy	20
4.2	Operational procedures for GTAC	21
4.3	Updated guidance for writing information leaflets for . . . those participating in gene therapy research	22

Section 5: GTAC PUBLIC MEETING – Decoding Childhood Gene Therapy.....	31
5.1 Summary	31
5.2 What the audience thought of the public meeting	32
5.3 Speakers’ biographies	33
5.4 Presentations.	34
Section 6: UPDATE OF CLOSED UK CLINICAL TRIALS	38
6.1 Cancer gene therapy trials	38
6.2 Human immunodeficiency virus (HIV) infection	56
6.3 Single gene disorders	59
Section 7: UPDATE ON GENE THERAPY WHITE PAPER COMMITMENTS	61
Section 8: ANNEXES	63
A. Glossary	63
B. Terms of Reference	73
C. Membership of GTAC	74
D. Register of Members Interests	76
E. External Expert Advisers to GTAC	78
F. Summary of UK Gene Therapy Trials 1993-2004	79

FOREWORD

Welcome to the Eleventh Annual Report of the Gene Therapy Advisory Committee (GTAC) which covers the Committee's work from January to December 2004.

For the past eleven years, GTAC has overseen the conduct of gene therapy clinical research in the UK. 2004 has been a particularly significant year. I was delighted that GTAC's good work was recognised in the new clinical trials regulations which came into force on 1 May 2004, naming GTAC as the UK national ethics committee for gene therapy research. It is the only specialist ethics committee mentioned in the regulations. From conversations with researchers, I understand that the idea of expert scientific and ethical review of clinical research proposals by one dedicated body is seen as a model for new and emerging technologies.

But is gene therapy really a "new" technology? It is now over a decade since the first gene therapy experiments were conducted in the UK and abroad. Looking back, the initial enthusiasm about the potential that lies in the concept of gene therapy has somewhat diminished and appears to have been followed by a sobering period of scepticism. I recall press articles of 2004 in which gene technologies were said to have been "over-hyped" and "oversold". Such scepticism is perhaps not fully justified. In fact, progress of gene therapy, slow as it might seem, appears to follow that of other biological medicines, such as monoclonal antibodies or recombinant proteins, which have taken decades to come to market. In 2004, GTAC has approved two late stage efficacy trials for the treatment of brain cancers. These trials are designed to compare gene therapy treatment with conventional treatments (such as chemotherapy), in order to assess in a properly controlled manner the advantages of one treatment with the other. This approach shows that gene therapy, in some situations is beginning to result in real clinical promise. You may be particularly interested in Section 6 of this report which gives summaries of completed UK clinical trials, which on the one hand, demonstrates the difficulties and lessons learnt, and on the other hand, highlights some of the achievements. There have been some successes. For example, immunotherapy in cancer treatment is beginning to show promise. While it is not possible to draw definite conclusions from small phase I trials, it is encouraging that some patients appear to have benefited from the experimental gene therapy treatment. In an early melanoma trial (GTAC 06), two patients remain well, following treatment, one of whom is disease free after ten years. Similarly encouraging results have been reported for the use of an oncolytic virus in brain cancer patients (GTAC 018), where a number of patients remain alive some 6 years after gene therapy.

We need to be realistic about what gene therapy has achieved so far and is likely to achieve in the near future. While there is no place for over-hyped optimism, one should not ignore the emerging successes. My view is that we are beginning to learn more and more about the circumstances in which gene therapy may ultimately provide an alternative treatment strategy. Different diseases are likely to require different approaches. Importantly, the potential of gene therapy has been recognised by the government in its 2003 Genetics White Paper. I hope that long-term public funding will continue and will allow the UK to maintain its position of leading Europe in gene therapy research.

GTAC's public meetings are designed to provide a forum, where gene therapy, problems and successes alike, is communicated to the interested public. The 2004 meeting in Cambridge's beautiful King's College attracted almost 100 attendees who heard several talks on gene therapy research in children. Building on the success of the 2003 meeting in Edinburgh, the day was extremely well received. The "GTAC road-show" continues! Our next public meeting is due to take place in Manchester on 3 April 2005, and all are welcome. Details of this event are on our website.

Finally, I wish to warmly thank everyone who, during 2004, has helped to ensure that UK gene therapy continued to be conducted to the highest possible standards of ethics and patient safety. GTAC's work would not be possible without input from all our advisers who have so generously contributed their time and expertise.

I trust you will enjoy reading this report.

Professor Norman Nevin, OBE
Chairman of GTAC
February 2005



SUMMARY

In 2004, the Committee considered in six committee meetings a total of twelve applications to conduct gene therapy clinical trials in the UK. Eleven applications were approved. The Committee also approved over 60 amendments to approved trials, and accepted three notifications for vaccination studies. Continuing the trend that over 70% of applications focus on cancer, the majority (seven) of 2004's approved applications were aimed at this disease, specifically colorectal cancer, prostate cancer, leukaemia, brain cancers, and advanced tumours. One application was an approach to combating HIV infection, and there were three applications to treat the various effects of coronary artery disease. See Section 1 for details and Section 2 for amendments to ongoing protocols.

An essential part of GTAC's business is to provide advice to researchers, to conduct horizon scanning activities of new developments in the field of gene therapy and to issue advice on these developments (Section 3).

One of the main challenges in 2004 was to ensure GTAC's compliance with the new Clinical Trials Regulations which came into force on 1 May 2004. In line with this, GTAC publishes operational procedures which give an account of how GTAC conducts its business. Over the reporting year, GTAC issued updated guidance on how to write a patient information leaflet and held a workshop on antisense technologies which led to a revision of its definition of gene therapy. See Section 4 for details.

Another essential aspect of GTAC's work is to inform the public of research involving gene therapy by holding annual public meetings. The 2004 meeting in July in Cambridge attracted around 100 attendees, who heard eight speakers talk about aspects of childhood gene therapy. Details of this well received event are given in Section 5.

Since 1993, GTAC has approved 96 clinical trials of gene therapy many of which are now closed for recruitment. To learn more about what these gene therapy trials have achieved and how results have helped to shape future trials, see Section 6 which provides short summaries of most closed trials.

June 2003 saw the publication of the Government White Paper: *Our Inheritance, Our Future – realising the potential of genetics in the NHS*. Of the £50 million to be spent on genetics in the NHS, over £10 million was specifically targeted at nurturing UK gene therapy. Section 7 describes progress made during 2004 with the implementation of the White Paper commitments.

As with any Committee's annual report there are also a number of Annexes. Of particular interest is Annex F which provides a summary and analysis of all UK gene therapy trials and compares UK gene therapy with research in Europe and worldwide.

SECTION I: PROTOCOLS REVIEWED BY GTAC IN 2004

In the reporting year, GTAC received twelve new applications (GTAC 74, GTAC 089 to 099) to undertake gene therapy clinical trials in the NHS. Of these twelve, ten were considered during committee meetings and two were approved by expedited review and Chairman's Action. One application was declined. The committee also received over 60 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 in the development of cancer are the cell's genes which can become damaged by a variety of factors such as the environment, diet and life-style. The chance of developing cancer can also be increased by an individual's genetic make-up, for example, in the case of familial breast and ovarian cancer, due to mutations in the BRCA and other genes. There are over 200 different types of cancer that can occur anywhere in the body. Surgery is usually the treatment of choice, however, cancer is less amenable to curative surgery once it has spread beyond the original tumour (metastasised). Gene therapy offers a new, but still experimental, potential treatment that could complement conventional treatments such as surgery, chemotherapy and radiotherapy. In fact, 72% of all gene therapy clinical trials in the UK aim to develop treatment for cancer (see Figure 3, Annex F).

Five of the eight studies described below use an "immunotherapy" approach to cancer (GTAC 089, 092, 095, 096, 098). Cancer cells carry on their surface markers that are recognisable to the immune system as "foreign", however, cancer cells do not trigger a strong immune response, rather they conceal themselves from the immune system. This is one explanation why cancer cells proliferate rapidly once established. Immunotherapy aims to boost the immune system's innate ability to recognise and destroy cancer cells.

Other approaches to cancer used in applications for trials in 2004 are gene directed enzyme prodrug therapy (GTAC 090) and the utilisation of oncolytic tumour specific viruses (GTAC 074, GTAC 094).

1.1.1 Prostate cancer

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

GTAC 089: A Phase III Trial of a DNA vaccine with a PSMA₂₇/ pDom fusion gene given by intramuscular injection in HLA A2+ patients with prostate carcinomas with or without electroporation

Prostate cancer is a possible target for immunotherapy because of well recognised cell surface and intracellular antigens. An antigen is defined as “anything that can be bound by an antibody” (usually a protein). Antibodies interact with small recognisable parts of the antigen known as “epitopes” and there usually is more than one epitope per antigen. The epitope used in this study is called PSMA₂₇, a short stretch of 9 amino acids (27 nucleotides) derived from the prostate cancer antigen PSMA (prostate specific membrane antigen). The gene therapy product consists of plasmid DNA which carries PSMA₂₇ fused to the gene for fragment C of tetanus toxin. This fragment, which is non-toxic, stimulates a strong immune response in the body. The product induces the production of immune cells (T cells) to act specifically against the pancreatic cancer cells. T cells, also called T lymphocytes, are white blood cells which coordinate the immune response.

A well known limitation of plasmid mediated gene therapy is the low efficiency of cellular uptake of the product. In order to assist this process, the study makes use of a technique called electroporation. Electroporation is the delivery of electrical pulses to destabilise the cell membrane so that large molecules such as plasmid DNA can enter the cell more easily. The effect of this is two-fold: Firstly, electroporation results in a higher concentration of plasmid in the cell. Secondly, this method is thought to enhance immunisation protocols in so far as the resulting stress on cells may provide a “danger signal” that attracts immune cells to the site.

Half of the patients on this trial receive the plasmid by simple intramuscular injection, the other half receive it by intramuscular injection with electroporation. This is to assess whether the DNA vaccine can induce a specific immune response against prostate cancer and whether this can be improved by using electroporation. The study was approved by GTAC in February 2004.

1.1.2 Brain cancers

The brain contains about 40 billion nerve cells, known as neurones, which are held in place and supported by glial cells. There are different types of glial cells, including astrocytes, oligodendrocytes and ependymal cells. Glioma is a general name for tumours that arise from this supportive tissue of the brain. Gliomas account for half of all brain tumours: there are approximately 29,000 cases of high-grade glioma per year in Europe, of which 16,000 are operable. Glioblastoma multiforme is a highly malignant form of glioma and the most common form of adult primary brain tumour. The outlook for patients with malignant gliomas is very poor. Current treatment consists of surgery followed by radio- and chemotherapy. Despite aggressive treatment the median survival for patients can be less than one year.

GTAC 090: A controlled, randomised, parallel group, multicentre study of the efficacy and safety of herpes simplex virus-thymidine kinase gene therapy (Cerepro™), with subsequent ganciclovir, for the treatment of patients with operable high grade glioma

This is a phase III study in patients with operable primary or recurrent high grade glioma. The design of this study is based on the results from two previous clinical studies which showed a significant increase in the median survival for patients. The study product is an adenovirus derived vector, called Cerepro, which contains the gene for the enzyme thymidine kinase (TK). Cells producing TK are susceptible to being killed by a drug called Ganciclovir: TK converts Ganciclovir into a toxic compound which induces cell death (apoptosis) in dividing cells. In principle, Cerepro can enter both dividing (tumour) and non-dividing (normal) cells in the brain; however, crucially, only dividing cells will be affected by Ganciclovir. Two hundred and fifty patients, at approximately 40 centres across Europe, will be randomised to either the active group, who will receive Cerepro and intravenous Ganciclovir, or the control group who will receive standard therapy alone. The study was approved by GTAC in April 2004.

GTAC 074: A randomised efficacy trial of herpes simplex virus HSV1716 in recurrent glioblastoma multiforme

The study product of this phase II/III trial is derived from Herpes simplex virus which causes infections such as cold-sores, genital infections and a rare brain infection (encephalitis). HSV1716 is a modified form of this virus which cannot infect cells that are not themselves rapidly dividing. Tumour cells, which are rapidly dividing, can therefore be infected by HSV1716 and it is this infection which is hoped will kill them. The study aims to assess the efficacy of HSV1716 administered by multipoint microinjection or convection enhanced delivery for the treatment of recurrent glioblastoma multiforme. HSV1716 has been used in a number of GTAC trials with encouraging results (see also Section 6). In this efficacy study, one hundred patients with residual or recurrent glioblastoma multiforme will be randomised to one of two treatment arms, HSV1716 treatment or chemotherapy treatment. The main objective is to determine whether HSV1716 is effective in the treatment of patients with recurrent glioblastoma multiforme compared to conventional chemotherapy treatments. This study, an outline of which had been submitted in 2003, was approved by GTAC in July 2004.

1.1.3 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 092: A 2 x 2 factorial randomised phase II trial assessing anti-CEA, anti-MUC-1 vaccination +/- chemotherapy +/- GM-CSF after surgery in patients with stage II colorectal cancer

As with most cancer trials, the approach is immunotherapy. The study product, called PANVAC, consists of 2 vectors, one derived from vaccinia virus and the other derived from

fowlpox virus. 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 F). The body reacts to infection with vaccinia virus with an immune response in an attempt to clear the ‘invader’. By contrast, fowlpox virus affects only avian species and, therefore, does not trigger a strong immune response in humans. Both vectors contain the same gene load, namely the tumour antigens carcinoembryonic antigen (CEA) and Mucin-1 (MUC-1), plus three co-stimulatory proteins which are not specific to colorectal cancer but are known to improve the potential for immune stimulation. PANVAC is used in the form of a so-called “prime-boost” regime. By ‘priming’ the immune system with the vaccinia product and then ‘boosting’ repeatedly with the corresponding fowlpox virus, it is hoped that the body’s anti-tumour response can be increased and prolonged. This regime will be used in patients with stage II colorectal cancer who have undergone curative resection of the tumour but it is expected that many patients will subsequently relapse. It is hoped that immunotherapy will prevent relapses in this type of patient with minimal disease. There are four treatment groups all of whom receive the gene therapy but some receive also chemotherapy and/or Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) which stimulates the growth and maturity of cells of the immune system known as dendritic cells. The main objectives of the trial are to assess T cell responses to PANVAC with or without concomitant chemotherapy and/or GM-CSF administration. The study was approved by GTAC in June 2004.

GTAC 095: Safety and immunology evaluation of TroVax produced by the Baxter synthetic route in patients with stage IV colorectal cancer

The TroVax product is used in a number of GTAC approved trials (GTAC 039, 077, 081, 087) but the product has been re-formulated. A clinical bridging study is necessary to assess the new product against the original formulation. TroVax is based on a virus called modified Vaccinia Ankara Virus (MVA, a member of the pox family, see also Figure 2, Annex F) to which the gene for “oncofoetal antigen”, or 5T4, has been added. 5T4 is found on the surface of cancer cells. The trial is an evaluation of TroVax in its new formulation in patients with metastatic colorectal cancer. The protocol was reviewed by expedited review and approved by Chairman’s Action in November 2004.

1.1.4 Breast cancer

Breast cancer usually affects in women but it can also occur also in men. It is the most common cancer in women, accounting for 30% of all cancers in women. 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 with approximately 80% of all breast cancers occurring 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 094: A Phase II exploratory study of the efficacy and safety of OncoVEX GM-CSF in combination with Arimidex in the neoadjuvant treatment of breast cancer in post menopausal women with oestrogen receptor positive tumours

OncoVEX is a Herpes Simplex Virus (HSV) vector used as a potential treatment of solid tumours. It has been used in the approved GTAC 062 clinical trial. OncoVEX results in the death of infected rapidly dividing cells such as cancer cells. This also causes the release of cancer proteins (antigens) from these cells, which can then be recognised by the immune system. The virus is engineered to produce Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) which stimulates the growth and maturity of dendritic cells. This further boosts the immune system. The study proposes to use OncoVEX as a treatment in post-menopausal women with breast cancer tumours that have a protein called “oestrogen receptor” (ER). Current therapies for these patients involve surgery, chemotherapy, radiotherapy and hormone therapy. Hormone therapy is used to shrink the tumour prior to surgery. The trial aims to compare the clinical response in patients who receive OncoVEX together with hormone therapy with patients who receive hormone therapy only. GTAC considered this trial at its September 2004 meeting and judged that there was insufficient data to make an ethical decision regarding the trial. The application was declined but the researchers were invited to resubmit once more data have been obtained.

1.1.5 Blood cancer (leukaemia)

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

GTAC 98: A pilot study of lentivirus transduced acute myeloid leukaemia (AML) blasts expressing B7.1 (CD80) and IL-2, for the induction of graft versus leukaemia (GVL) effect in poor prognosis, relapsed AML

There are about 2,000 cases of adult acute myeloid leukaemia in the UK each year. In older patients, up to 70% achieve complete remission or good partial remission after chemotherapy. However, relapse is almost universal and the possibility of long-term disease free survival is only about 10% with 5% of patients surviving for more than 3 years. Because of these statistics, post-remission therapy in this older group of patients remains a difficult area. The only long-term cure is provided by a bone marrow transplant from a compatible donor (allogeneic transplant) in which the therapeutic effect is mainly due to a graft-versus-leukaemia effect (GvL). This is when the transplanted donor cells launch an immune attack against the patient’s leukaemic cells and destroy them. GvL is further enhanced by additionally infusing the patient with leukocytes (immune cells) from a compatible, healthy donor, which also have the ability to attack and kill the leukaemic cells. A recognised problem of allogeneic transplants (or grafts) is graft-versus-host disease (GvHD). This occurs when the transplanted bone marrow cells give rise to immune cells that can attack the patient’s healthy cells.

This study is targeted at poor prognosis patients who have received post-remission chemotherapy and a bone marrow transplant but who are showing defined signs of relapse. The main objective of this study is to stimulate a more effective graft-versus-leukaemia effect. Patients' peripheral blood cells which contain leukaemic cells are removed (prior to post-remission chemotherapy and bone marrow transplant) and infected *ex vivo* with the study product. Modified cells are lethally irradiated before being returned to the patient after he/she has received chemotherapy and a bone marrow transplant and has shown signs of relapse. The study vector is derived from Human Immunodeficiency Virus (HIV, a lentivirus) from which all viral genes have been removed. Instead, the vector carries the genes for two proteins: interleukin-2 (a protein that activates the function of T cells of the immune system) and CD80. CD80 is found on the surface of cells of the immune system called antigen presenting cells. These stimulate the immune system, in particular T cells. Infecting patients' leukaemic cells with CD80/IL-2 makes the cells more recognisable to grafted, healthy, immune cells (from the donor) which can then mount an effective immune response against the leukaemia. The study aims to determine whether lethally irradiated modified leukaemic cells are able to stimulate the GvL effect and prolong the duration of remission. The study was approved by GTAC in November 2004.

1.1.6 Multiple cancers

GTAC 96: A phase I study of adoptive transfer of autologous tumour antigen-specific T cells with pre-conditioning chemotherapy and intravenous IL2 in patients with advanced CEA positive tumours

This study involves a regime of gene therapy and chemotherapy for patients with CEA positive cancers. Carcinoembryonic antigen (CEA) is a protein that is present on the cell surface of a number of tumours, including bowel, stomach and pancreatic cancer (see also GTAC 092). The study product is a retroviral vector which contains two genes for an antibody fragment against CEA and the ξ protein of CD3. CD3 is a protein complex on the surface of T cells. It is made of 5 individual proteins one of which is the ξ protein. Binding of ξ to antigens (here: CEA) activates the T cell and immune system. Patients' T cells are exposed in the laboratory to the study vector (*ex vivo*). Modified cells are re-infused back to the patient in the hope that these cells will mount an immune attack against CEA positive cancer cells. Prior to infusion of the T cells, pre-conditioning therapy (chemotherapy) is used to reduce the number of unmodified T cells and to enable the expansion of the modified therapeutic T cells. Patients also receive infusions of interleukin-2 to promote the survival and proliferation of therapeutic T cells. The main objectives of this trial are to evaluate the feasibility and safety of this approach and to determine the survival and toxicity of modified T cells given with chemotherapy and interleukin-2. The study was approved by GTAC in November 2004.

1.2 CARDIOVASCULAR DISEASE

1.2.1 Coronary artery disease

The coronary arteries can become narrowed by a gradual build-up of fatty material within their walls. This can result in a reduction of oxygen-containing blood to the heart muscle when demands are high (such as during exercise). The pain or discomfort that results is

called angina and it is due to the lack of oxygen reaching the heart muscle. The standard treatments for angina are drugs that are aimed at improving blood flow to the heart muscle or more invasive treatments such as balloon angioplasty. This involves inserting a catheter with a balloon at its tip into an artery and advancing it to the narrowed part of the artery. When the balloon is inflated it squeezes the fatty plaque deposit, opening the narrowed artery. In more severe cases coronary artery bypass surgery is required.

GTAC 097: A multicenter, randomised, double-blind, placebo-controlled study evaluating the efficacy of BIOYPASS (ADGVVEGF121.10NH) delivered by NOGA™ – Guided/ myostar catheter in no option patients with class II-IV stable angina

This study is aimed at so-called ‘no-option’ angina patients who, after medical treatments, continue to suffer from moderate to severe angina and who are not candidates for established re-vascularisation procedures or coronary bypass grafting. The study vector is derived from adenovirus, engineered so that it can no longer replicate or produce infectious virus. The virus can, however, efficiently target non-dividing, terminally differentiated heart muscle cells. It contains the gene for vascular endothelial growth factor (VEGF), a protein which stimulates new blood vessel growth (or angiogenesis). Therapeutic production of VEGF is achieved by injecting the vector directly into the heart muscle (intramyocardially) via a heart catheter which is passed into a coronary artery by insertion into an artery in the groin or arm. The main objective of this study is to assess the effect on exercise tolerance when compared to placebo. The study was approved by GTAC in November 2004.

1.2.2 Peripheral artery disease

Arteries are the blood vessels that take oxygen-rich blood from the heart to all parts of the body. Peripheral artery disease (PAD) is a common problem in late middle age, leading to severe pain on walking, tissue breakdown and ulceration, loss of toes due to gangrene, and limb amputation. This disease is caused by arteriosclerosis (fatty like deposits in the arteries) resulting in narrowing of the arteries reducing the amount of oxygen reaching the extremity of the limb. The decrease of oxygen supply to the tissues (ischemia) causes pain on exertion. People with PAD are also likely to have narrowing of other arteries in the body. If there is narrowing in the arteries which supply blood to the heart, it can cause angina or a heart attack (see 1.2.1). If the arteries to the neck are affected, it can interfere with the flow of blood to the brain and may cause a stroke.

Patients with PAD in the leg frequently suffer from claudication. Claudication is defined as the reproducible muscle pain which is caused by inadequate blood flow to the leg. It is one of the most common symptoms of PAD. Claudication occurs during physical activity and is relieved after a short rest. Although often amenable to vascular surgery, many patients are not suitable because the vessels affected are too small to bypass or because the patient is unfit for an operation. An alternative strategy is to persuade the limb to grow more blood vessels by injecting a gene which stimulates blood vessel growths. A number of growth factors have been shown to be capable of inducing the growth of new blood vessels: vascular endothelial growth factor (VEGF, see GTAC 097) and fibroblast growth factor I (FGF-I as in GTAC 054 and 091).

GTAC 091: Double-blind, randomised, placebo-controlled, parallel group and dose-finding, multicentric, safety and efficacy study with intramuscular injections of NVIFGF in subjects with intermittent claudication

In this study in patients with intermittent claudication, fibroblast growth factor 1 (FGF-1) is delivered to the muscle by an injection of a DNA plasmid carrying the FGF1 gene (the same product is used in the GTAC 054 study). The study is based on a phase I clinical study that demonstrated no serious adverse events attributable to the treatment. Although designed as a safety trial, there was some clinical benefit with reduction in ulcer size and lessening of pain at rest. These encouraging results formed the basis of the new study. The plasmid DNA, or placebo, are injected intramuscularly into the leg at various points. Effectiveness is evaluated by measuring the total distance patients can walk on a treadmill test, by assessing the formation of new blood vessels and by quality of life assessments. The protocol was reviewed by expedited review and approved by Chairman's Action in April 2004.

GTAC 099: A phase 2, randomized, double-blind, placebo controlled, parallel-group, multicenter, dose-selection study of Ad2/hypoxia inducible factor HIF-1 α /VP16 in patients with intermittent claudication

This trial, also in patients with intermittent claudication, uses hypoxia induced factor-1 α to induce therapeutic “angiogenesis” (vascularisation of a tissue involving the development of new blood vessels). HIF-1 α encodes a transcription factor, which means that it operates like an on-off switch for other genes. HIF-1 α is produced at elevated levels when there are low oxygen levels in the muscle tissue (hypoxia). This induces the production, amongst others, of angiogenic growth factors which then stimulate the growth of new blood vessels and potentially increase the flow of oxygenated blood to these cells. Examples of such growth factors are vascular endothelial growth factors (VEGF or FGF-1, see GTAC 097 and 091 respectively). The HIF-1 α gene is delivered by an adenoviral vector. Also produced by the product is a protein derived from herpes simplex virus called VP16 which is thought to activate the HF-1 α gene. As with GTAC 91, this study is based on encouraging results from phase I studies which showed that the product is well tolerated and that there was some clinical improvement in some patients. In the new study, patients receive injections of the gene therapy product or a placebo by injections into the muscle of both legs. The main objective is to assess the treatment at various doses compared to the placebo. If successful, this will provide the basis for optimal dose selection for phase III studies. The study was approved by GTAC in November 2004.

I.3 HUMAN IMMUNODEFICIENCYVIRUS (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 CD4 protein receptor which is produced on the surface of these cells allows HIV to attach, enter and thus infect the cell. This results in a loss of immune function which 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. At the end of 2003, an estimated 53,000 adults aged over 15 were living with HIV in the UK.

Highly active anti-retroviral therapy (HAART) has resulted in significant clinical benefit for HIV positive patients. HAART is aimed to suppress HIV replication and to increase CD4 T cell numbers, partially restoring the body's immune response to opportunistic infections. However, there are difficulties associated with HAART, for example the emergence of drug resistant HIV variants and HAART toxicity.

GTAC 093: An open, randomised, parallel group study to evaluate the safety, tolerability and immunogenicity of the GW825780 DNA immunotherapeutic when delivered using the Powderject ND5.5 device to healthy adult volunteer subjects

As with most gene therapy approaches against HIV, this phase I study aims to stimulate T cell responses to the HIV. It is hypothesised that patients who develop a robust T cell response to HIV soon after exposure may be able to control infection, especially if helped by HAART drugs. In order to assess the safety of such an approach, this phase I study is conducted in healthy adult volunteers. It sets out to identify the most appropriate dose and scheduling for delivery of the DNA vaccine for future trials in HIV positive individuals. The study product is plasmid DNA which is coated onto the surface of microscopic gold particles which are then projected into the skin by using a helium pressurised delivery system. The DNA contains multiple HIV antigens derived from three HIV proteins. Each antigen contains more than one immune recognisable stretch (epitope) giving rise to as many T cell populations as there are epitopes. It is hoped that this will enable an effective immune response even if not all epitopes remain active – the HIV virus is known to mutate rapidly to avoid recognition of epitopes by the host immune system. The study was approved by GTAC in May 2004.

SECTION 2: AMENDMENTS TO ONGOING PROTOCOLS

ENROLMENT INTO GENE THERAPY TRIALS FOR IMMUNODEFICIENCIES AT GREAT ORMOND STREET HOSPITAL, LONDON

Immunodeficiencies are diseases due to an inability of the body to mount a normal immune response. Immunodeficiencies can be due to a genetic disease or acquired as in AIDS due to infection with HIV. Severe Combined Immune Deficiency (SCID) is the name given to a group of genetic diseases of the immune system. There are three gene therapy clinical trials in the UK which aim to treat genetic immunodeficiencies, namely for X-linked severe combined immunodeficiency syndrome (X-SCID, GTAC 045), adenosine deaminase deficiency (ADA-SCID, GTAC 073) and chronic granulomatous disease (CGD, GTAC 046).

X-SCID is an inherited disorder that affects boys rendering them highly susceptible to infections with bacteria and viruses. 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 on the X chromosome) 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.

ADA-SCID is an immune deficiency which can affect both boys and girls. Adenosine deaminase is a metabolic enzyme, the gene of which is located on chromosome 20. In ADA-SCID patients, both parental copies of chromosome 20 contain faulty forms of the ADA gene. Loss of ADA hampers the development and function of progenitor cells of the immune system called lymphoid cells. These cells develop into T lymphocytes that attack virally-infected cells and cancer cells, and B lymphocytes that produce antibodies to fight infection. As ADA-SCID patients have only limited numbers of T and B lymphocytes, they have an impaired ability to fight infection.

Chronic granulomatous disease (CGD) is a group of rare, inherited disorders of the immune system due to defects in immune system cells (phagocytes). These defects leave patients vulnerable to severe recurrent bacterial and fungal infections and chronic inflammatory conditions such as gingivitis (swollen inflamed gums), enlarged lymph glands, or tumour-like masses called granulomas. In CGD, the granulomas form when white blood cells continue to collect in infected areas even after antibiotics have eliminated the infection. This happens because the defective CGD phagocytes cannot generate the oxygen compounds that normally help shut down the body's immune defences. While not malignant, granulomas can cause serious problems by obstructing passage of food through the oesophagus, stomach, and intestines as well as blocking urine flow from the kidneys and bladder.

Applications to enrol new patients into the above gene therapy studies 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 in France had developed a leukaemia-like illness following retroviral X-SCID therapy. Five applications to treat new patients with gene therapy were received in 2004. These concerned the treatment of two patients with X-SCID, two patients with chronic granulomatous disease and one

patient with adenosine deaminase deficiency. After careful consideration of all 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, GTAC approved the treatment of the two patients with X-SCID (cleared by correspondence) and the two CGD patients (November Committee meeting). In the case of the ADA-SCID patient, the committee deferred its decision for clinical reasons.

SUMMARY OF SUBSTANTIAL AMENDMENTS TO TRIALS DISCUSSED DURING COMMITTEE MEETINGS

GTAC 055: Gene directed enzyme prodrug therapy for the treatment of prostate cancer

The protocol utilises gene directed enzyme prodrug therapy for prostate cancer. Solid tumours are injected with the study product, which contains the gene of a pro-drug-converting enzyme called nitroreductase. Following delivery of the gene therapy, patients are dosed with the pro-drug (CBI954). Those tumour cells which have taken up the product and produce nitroreductase, convert the pro-drug to a toxic form which causes the death of the cancerous cells. Two substantial amendments to the study were considered. The first was a revision of the level of liver toxicity at which dose limiting toxicity would be triggered and was approved by GTAC in February 2004. The second amendment asked GTAC to consider approving the administration of second rounds of treatment to patients enrolled into the therapeutic arm of the trial. The amendment was approved by GTAC in November 2004.

GTAC 053 and 079: Pilot studies of the safety and immunogenicity of vaccines pTHr.HIVA or MVA.HIVA in HIV-1-seropositive subjects receiving highly active anti-retroviral therapy

In 2004, recruitment into the above two trials (and similar studies in healthy volunteers) was temporarily interrupted voluntarily by the researchers. This was a response to unusual results from pre-clinical studies with related study products. After consideration of these findings and their relevance for the above trials in June 2004, GTAC concluded that there were no safety concerns with the pTHr.HIVA and MVA.HIVA products. Recruitment into the trials recommenced shortly thereafter.

GTAC 018: A Phase I dose-escalation study of intratumoral injection with modified HSV Type I (ICP 34.5-) into primary and recurrent malignant glioma

An application for compassionate use of HSV1716 in a patient with recurrent glioblastoma multiforme according to the protocol of this (closed) trial was considered and approved by GTAC in April 2004. See also Section 6 for a summary of the GTAC 018 trial, and Section 1.1.2 for details of a new phase II/III trial with HSV1716 (GTAC 074).

SUMMARY OF MINOR AMENDMENTS TO TRIALS AND ISSUES PROCESSED BY CHAIRMAN'S ACTION

In 2004, GTAC received 62 applications to amend ongoing studies, of which 61 were approved. They are listed below.

January to February

- GTAC 087: Final approval of this cancer study.
- GTAC 051: Two approval letters relating to the Papworth Hospital site of this study.
- GTAC 055: Approval to open a new study centre in Leeds.
- GTAC 055: Approval to dose escalate in the operable arm of the prostate cancer study. This is designed to determine potential therapeutic levels of transgene expression.

February to April

- GTAC 072: Approval of amendment 4 of this melanoma trial. This permits recruitment of an additional cohort of 5 patients to allow better assessment of the prime-boost regime, plus a minor amendment to the exclusion criteria and immunisation procedure.
- GTAC 084: Approval of a number of minor changes made to this melanoma trial.
- GTAC 086: Approval of amendment 1 of this melanoma trial relating to the time when tumour biopsies are taken.
- GTAC 077: Approval of amendment 1 of this colorectal cancer trial to increase the number of patients from 15 to 20.
- GTAC 077: Approval of amendment 2 which concerned an additional patient information leaflet and consent form to ask patients for permission to test old tumour biopsy samples.
- GTAC 083: Approval of amendment 1 of this pancreatic cancer trial relating to the infusion of the pro-drug
- GTAC 062: Approval of amendment 9 which proposed positron emission tomography as an additional investigational technique to computed tomography.
- GTAC 058: Approval of a revised patient information leaflet for this breast cancer trial.
- GTAC 088: Approval of amendment 1 which clarified a number of procedures and tests performed during the trial.
- GTAC 055: Approval to dose escalate in the inoperable arm of this prostate cancer study.

GTAC 091: Conditional approval of the trial in subjects with intermittent claudication.

GTAC 045: Approval to enrol a new patient into the X-SCID trial.

April to June

GTAC 044: Approval of an updated patient information leaflet for this study of donor lymphocytes in leukaemia patients.

GTAC 044: Approval of amendment 2 of this melanoma trial which concerned the patient information leaflet and patients' option to consent to an additional biopsy.

GTAC 091: Full approval of this study in subjects with intermittent claudication.

GTAC 055: Approval to retreat a patient on this prostate cancer trial.

GTAC 084: Approval to retreat a patient on this melanoma trial.

GTAC 089: Approval of amendment 1 of this prostate cancer trial which related to the wording in the protocol and patient information leaflet on indemnity.

June to July

GTAC 055: Approval to retreat a patient on this prostate cancer trial.

GTAC 089: Approval of a small amendment to the inclusion criteria of this prostate cancer trial.

GTAC 066: Final approval of this carcinoma trial which follows conditional approval given in February 2002.

GTAC 054: Approval of a small amendment which concerned the analysis of safety and efficacy data of all patients treated so far.

GTAC 091: Approval of several administrative amendments to the intermittent claudication trial. Permission to test patients for the presence of anti-FGF-1 antibodies was given.

GTAC 062: Approval of an additional co-investigator at St George's Hospital.

GTAC 060: Approval of an amendment to this breast cancer trial.

GTAC 29B: Approval of several small amendments to this "educated donor lymphocytes" (EDLI) trial.

GTAC 29C: Approval of several small amendments to idiotype vaccination for multiple myeloma trial (MMIFTT).

GTAC 087: Approval of amendment 1 which comprised of several small changes.

July to September

- GTAC 091: Approval of a new study site, the Freeman Hospital, Newcastle.
- GTAC 083: Approval of a third study site, the Christie Hospital, Manchester.
- GTAC 085: Approval of amendment 1 of the HIV study. This concerned several clarifications as well as the inclusion of data from the sister GTAC 75 trial.
- GTAC 093: Approval of amendment 1 of this HIV study. This introduced an assessment of pain at the vaccination site.
- GTAC 055: Approval to dose escalate the adenoviral vector in the operable arm of this prostate cancer trial.
- GTAC 055 : Approval to retreat a patient in the inoperable arm of the trial.
- GTAC 084: Approval to retreat a patient.
- GTAC 076: Approval of version 2 of the carcinoma trial which is now under new sponsorship.
- GTAC 088: Approval of amendment 2 (clarifying changes to the trial protocol).
- GTAC 079: Approval of amendment 1 of the HIV trial in sero-positive subjects. Ten patients from an earlier HIV trial are to be included into the study.
- GTAC 055: Declination of the request to retreat a patient.

September to November

- GTAC 076: Approval of an amended patient information leaflet.
- GTAC 055: Approval to escalate the dose of virus particles in the inoperable arm of the trial.
- GTAC 087: Approval of an amendment to extend the period of the baseline CT scan.
- GTAC 093: Approval of a summary information leaflet which is to be sent to potential volunteers as initial information about the trial.
- GTAC 066: Approval of revised patient information leaflet.
- GTAC 083: Approval of revised patient information leaflet.
- GTAC 047: Approval of King's College Hospital to become new trial site.
- GTAC 092: Final approval of the study.
- GTAC 045: Approval to enrol a new patient into the X-SCID trial.

November to December

GTAC 084: Approval to retreat a patient with melanoma.

GTAC 089: Approval of an amendment to the patient information leaflet.

GTAC 095: Approval of the cancer study.

GTAC 065: Approval of an updated protocol and Patient Information Leaflet.

GTAC 068: Approval of an updated protocol and Patient Information Leaflet.

GTAC 085: Approval of amendment 2 of the trial which related to indemnity and a small change to the exclusion criteria.

GTAC 095: Approval of amendment 1 of the colorectal cancer study.

GTAC 072: Approval of an amended patient information leaflet in view of an interim safety report.

SECTION 3: GUIDANCE ISSUES

3.1 ADVICE TO RESEARCHERS

In its function as the national ethics committee for gene therapy research GTAC provides advice to researchers on issues of clinical trials of gene therapy, for instance, on the content of future proposals for gene therapy research on human subjects, on the appropriate design and conduct of the proposed research, on the facilities necessary for the proper conduct of the research and on arrangements necessary for appropriate patient information and consent.

In this capacity, in 2004, GTAC had formal discussions with two teams to provide them with guidance on their work. These were Oxford Biomedica who sought GTAC's opinion on a proposed study in patients with Parkinson's disease, and with the Institute of Child Health regarding a future trial of gene therapy for cystic fibrosis in children. In this context, GTAC would like to thank Dr K Ray Chaudhuri, of Kings College London and Lewisham Hospitals for his expert advice regarding Parkinson's disease.

Building on this long standing successful arrangement, GTAC encourages researchers who have in mind new clinical gene therapy studies to come forward for an early discussion with the committee, particularly in cases where the trial may involve novel and potentially controversial aspects.

3.2 HORIZON SCANNING ACTIVITIES

In order to be aware of different developments relevant to gene therapy clinical research, GTAC invites external speakers to brief members on new advances. In the reporting year, there were two presentations to the committee.

In April 2004, Mr Hugh Whittall of the Department of Health's Human Tissue Policy Section gave a talk to GTAC on the Human Tissue Bill, and in September, Mr Richard Walsh, Head of Health, Association of British Insurers, spoke about insurance and clinical trials. The speakers have kindly provided the following abstracts of their presentations.

The Human Tissue Bill (Mr Hugh Whittall)

The purpose of the Human Tissue Bill is to provide a consistent legislative framework for issues relating to whole body donation and the taking, storage and use of human organs and tissue. It will make consent the fundamental principle underpinning the lawful storage and use of human bodies, body parts, organs and tissue and the removal of material from the bodies of deceased persons.

It will set up an over-arching authority which is intended to rationalise existing regulation of activities like transplantation and anatomical examination, and will introduce regulation of other activities like post mortem examinations, and the storage of human material for education, training and research. It is intended to achieve a balance between the rights and expectations of individuals and families, and broader considerations, such as the importance

of research, education, training, pathology and public health surveillance to the population as a whole.

The Bill repeals and replace the Human Tissue Act 1961, the Anatomy Act 1984 and the Human Organ Transplants Act 1989 as they relate to England and Wales, and the equivalent provisions in Northern Ireland.

Clinical trials and health insurances (Mr Richard Walsh)

The UK health and protection insurance market is entirely commercial. It is voluntary and insurers price based on risk assessment. The underlying assumption is disclosure of all relevant information by applicants to insurers and insurers assessing risk based on the evidence. This is in contrast to social insurance – where underwriting is restricted by the State and obtaining cover is often compulsory. Each type of insurance has a different kind of risk dynamic and these can be classified into first layer risks; for example age, gender and smoking status, and second layer risks; for example medical history, family history and occupation. With better medical and epidemiological evidence, terms can be quoted for lives that were previously considered uninsurable.

Some clinical trials are on healthy individuals. Other are on ill people to test out new treatments. Some trials are randomised controlled trials (RCTs), where neither the patient nor the doctor knows if the patient is receiving treatment. Others are longitudinal cohort studies – essentially regular screening checks on a defined population. In the case of screening and pre-trial screening a condition may be discovered which a person was unaware of. This would need to be disclosed, as would the result of any other medical diagnostic test. The exception is predictive genetic tests, which are covered by a moratorium. Assuming no new diagnosis two situations may arise:

- Healthy people on a clinical trial – involvement does not bring about any additional risk, and even if it did the individual would not know they were receiving an active ingredient. There is therefore no quantifiable risk or inequality of information and no effect on premiums. People volunteering for trials are not regarded as “risk takers” – such activity is not like sky-diving – if it was it would never get ethical approval.
- Trials on ill people – insurers would assess risk (and rate) based on pre-existing conditions and being on a trial would not mean that the person was any more or less ill. Sometimes Private Medical Insurance will fund such trials. If the trial results in cure or stabilisation the patient may benefit from better terms as they could from any other successful medical treatment.

In summary, people (whether healthy or not) entering clinical trials need not worry about the insurance implications of the trial itself. Even in the case study presented on HIV vaccine there was no impact on insurance premiums.

3.3 LENTIVIRAL SAFETY

During 2004, GTAC received and reviewed reports which potentially called into question the safety of some research vectors based on lentiviruses. Lentiviruses are a subgroup of retrovirus. There are many different lentiviruses, some infect humans, others infect animals. An example of a human lentivirus is Human Immunodeficiency Virus (HIV), the virus that causes Acquired Immunodeficiency Syndrome (AIDS). When used as a gene therapy vector, the virus is modified to make it safe for use by removing its ability to cause AIDS. Because lentiviral gene therapy vectors can integrate into a person's DNA and are therefore long lasting, researchers hope that they can be developed into a stable and efficient means of delivering gene therapy.

A GTAC subgroup was formed to discuss the information received. The subgroup comprised of Prof Norman Nevin (Chair), Prof James Neil, Prof Andrew Lever, Prof David Harrison, the GTAC Secretariat, and representatives of the Health and Safety Executive (HSE) as observers. The subgroup met twice with the parties involved, analysed the information and reported back to GTAC with its conclusions and recommendations. Based on this assessment, GTAC took the following action.

In order to alert the international gene therapy research community of GTAC's concerns regarding the application of some lentiviral vectors under certain conditions, on 5 November 2004, GTAC sent an open letter (overleaf) to international regulators of gene therapy, gene therapy professional bodies, and the UK gene therapy research community.

Additional information was subsequently released by the Health and Safety Executive "The Scientific Advisory Committee on Genetic Modification (Contained Use) Information Note Concerns about the safety of some viral vectors" (see: <http://www.hse.gov.uk/aboutus/meetings/sacgmcu/index.htm>). Responses to GTAC's Open Letter were made by the European Society of Gene Therapy (ESGT, see: <http://www.esgt.org>), by the Paul-Ehrlich-Institut, the German Federal Agency for Sera and Vaccines (see <http://www.pei.de> or http://www.pei.de/downloads/commentary_lentiviral_vectors.pdf) and by the British Society for Gene Therapy (<http://www.bsgt.org>).

At the time of print, there was no further information available.

GTAC

Gene Therapy Advisory Committee

<http://www.advisorybodies.doh.gov.uk/genetics/gtac/>

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

To Whom It May Concern

5 November 2004

Dear Colleague

The UK Gene Therapy Advisory Committee (GTAC) has concerns regarding the safety of some lentiviral gene therapy vectors

I am writing as the Chairman of the Gene Therapy Advisory Committee, the UK national supervisory body for clinical gene therapy research, to inform you of certain matters regarding some lentiviral vectors.

As part of GTAC's horizon scanning activity, reports have been received of the development of liver tumours in a pre-clinical study using lentiviral vectors. Most of the tumours occurred in a group of mice that had been treated *in utero* with a vector carrying the factor IX gene, although a small number of tumours were also observed in animals that had been treated neonatally or had received vectors carrying only marker genes. Experiments are ongoing to investigate the precise nature of the tumours and the mechanism of induction. Although the number of mice involved is small and the wider implications are not yet clear, GTAC considers that the gene therapy community should be alerted to these observations in case these have a bearing on pre-clinical screening or clinical studies that are planned or in progress outside the UK. These observations do not appear to affect any current or previous UK trials.

GTAC is keeping the current situation under review and hopes that relevant results will be published shortly. If substantial new information becomes available which concerns the gene therapy community, GTAC will issue advice as appropriate.

Should you have any further questions or concerns, please write to the GTAC Secretariat at gtac@dh.gsi.gov.uk.

Yours Sincerely,



PROFESSOR NORMAN C NEVIN, OBE
GTAC CHAIRMAN

SECTION 4: REGULATORY ISSUES

4.1 WORKSHOP ON ANTISENSE TECHNOLOGIES AND REVIEW OF GTAC'S DEFINITION OF GENTHERAPY

In May 2004, GTAC organised a workshop on antisense technologies to inform members about this emerging technology and for the committee to discuss how to assess applications concerning antisense products in future.

In the morning, three educational talks were given to provide the committee with some additional background on various issues and techniques to do with antisense technologies. The three speakers and their talks were:

- Professor Finbarr Cotter, Barts and The London School of Medicine: “Antisense”
- Dr Matthew Wood, Department of Human Anatomy & Genetics, Oxford University: “RNA interference: Biology and Application”
- Professor George Dickson, School of Biological Science Royal Holloway, University of London: “Gene Correction Strategies via Antisense Modulation of Pre-mRNA Splicing”

This was followed by an afternoon policy session to discuss questions relating to the range of possible antisense therapies that may be used in clinical trials. These were as follows:

1. Synthetic antisense oligonucleotides to down-regulate the expression of undesired proteins (gene silencing). Synthetic antisense oligonucleotides are used widely in phase I to III clinical trials, primarily in cancer trials and against infectious diseases, such as HIV or hepatitis. GTAC decided that all antisense applications should be reviewed by GTAC. There should be a procedure for expedited review of applications which use established methodologies. Applicants of antisense trial should be given the opportunity to request exemption from the DH Flagging Project, provided an appropriate justification can be given.
2. Length of molecule and degree of chemical modification. Most oligonucleotide compounds used in clinical trials are between 15 and 25 bases long. These compounds are chemically modified to make them more resistant to biological degradation. GTAC decided that all applications using synthetic oligonucleotides irrespective of length or degree of chemical modification should be reviewed by GTAC.
3. Antisense DNA/RNA expressed in vivo via an expression vector. In contrast to synthetic antisense products, the active compound is not delivered directly but it is produced in the body by means of an expression vector. GTAC decided that all applications using an expression vector for antisense DNA or RNA should be reviewed by GTAC, and should be subject to the DH Flagging Project.
4. Synthetic antisense oligonucleotides to modify a gene (gene correction). In this scenario, antisense molecules are not being used to suppress protein expression but to modulate a gene. GTAC decided that applications of antisense oligonucleotides for

gene correction or modification purposes should be reviewed by GTAC, and should be subject to the DH Flagging Project.

5. Interference RNA and other new technologies (such as ribozymes). These strategies are largely at the research stage, and not likely to go into clinical trials in the next few years. Nevertheless, GTAC decided that any application of RNAi, or other new DNA or RNA technologies in the form of clinical trials, should be reviewed by GTAC.

As GTAC had clarified its position on antisense technologies, a rewrite of GTAC's definition of gene therapy, and accompanying list of inclusions and explanations, became necessary. The final agreed definition is as follows:

“The deliberate introduction of nucleic acids into human somatic cells for therapeutic, prophylactic or diagnostic purposes.”

This definition is intended to incorporate all clinical trials involving the use of techniques for delivering synthetic or recombinant nucleic acids (DNA and RNA) into human subjects. Such techniques include, but are not limited to, the use of:

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

This definition is reproduced in GTAC's operational procedures (see Section 4.2).

4.2 OPERATIONAL PROCEDURES FOR GTAC

The introduction of the Medicines for Human Use (Clinical Trials) Regulations 2004 required GTAC to review its operational procedures as the national ethics committee for gene therapy clinical trials. This is an evolving document and researchers are encouraged to consult the GTAC website for the most up to date version. See: <http://www.advisorybodies.doh.gov.uk/genetics/gtac/publications.htm>.

The document gives guidance on the procedures that should be followed in the United Kingdom when proposals are made to conduct gene therapy research on human subjects. It details the information that should be submitted in order to enable GTAC to assess the acceptability of gene therapy research proposals. It also sets out GTAC's practices and

procedures to meet its obligations as the national research ethics committee for gene therapy clinical research, in accordance with the clinical trials regulations. It is a legal requirement that all UK gene therapy clinical research be submitted to GTAC and no clinical gene therapy research should commence in the absence of GTAC's written approval.

Supplementary guidance and reports have been issued by GTAC in relation to monitoring of patients enrolled in adenoviral gene therapy studies and in utero gene therapy. Both can be obtained as stand-alone documents from the GTAC website (<http://www.advisorybodies.doh.gov.uk/genetics/gtac/publications.htm>).

4.3 UPDATED GUIDANCE FOR WRITING INFORMATION LEAFLETS FOR THOSE PARTICIPATING IN GENE THERAPY RESEARCH

In 2004, GTAC also revised its guidance for researchers on the writing of patient information leaflets. This can also be found on GTAC's website (<http://www.advisorybodies.doh.gov.uk/genetics/gtac/publications.htm>).

1. The following is based on guidance first issued in 1995. It provides more detailed advice for those with clinical responsibility for participants and those with responsibility for the design of gene therapy trials. This guidance should be read with the sources of general advice on patient information and consent, for example COREC's guidelines for researchers on writing a patient information leaflet and consent form (<http://www.corec.org.uk/applicants/index>): "Guidelines for researchers: patients information sheet & consent form", the Patient Advice and Liaison Services (PALS, <http://www.nelh.nhs.uk/pals/>), and CancerHelp UK, the patient information website of Cancer Research UK (www.cancerhelp.org.uk).

Researchers are asked to familiarise themselves with guidance on the storage and use of remaining samples from patients, as issued by the Department of Health (see http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4008473&chk=CCTuGI). New guidance will be provided following the implementation of the Human Tissue Bill.

Informing Patients

2. Enabling the potential subjects of research to make a decision whether or not they might participate is one of the most important aspects of the ethical acceptability of research. They must be well informed about the procedures and risks of the protocol and the responsibilities that they are being asked to take on. This is true of all medical research which involves human subjects, but is especially so in the field of gene therapy. Not only is the topic unusually complex, but there is likely to be a need for long term follow up.
3. Although information can be given in a number of ways, the written information leaflet is particularly important and should always be provided. It is a permanent record of the key points of any research trial, to which the patient can refer, and therefore a critical element in informing consent. The document also provides a source of reference for

families and friends. In addition it gives GTAC an opportunity to assess this aspect of the research protocol.

General Principles

4. There is no single correct way of writing information for patients. The aim must be to present sufficient, but not excessive, information in a form that is understandable. This calls for thoughtful and tested use of language, vocabulary and presentational techniques.
5. Understanding, and recall, of what to many patients will seem to be complex information, are reduced by anxiety, poor presentation and the use of complex language, technical terms and jargon. Conversely, understanding and recall are enhanced by:
 - keeping the format simple and sentences and paragraphs short, so that it can be read and re-read at leisure;
 - using of plain English and simple words;
 - making only one point in each sentence;
 - using illustrations where appropriate;
 - avoiding crowding pages with too much information and keeping plenty of space;
 - ensuring that other modes of communication, such as counselling, reinforce and amplify the written information, but do not contradict it;
 - avoiding technical terms whenever possible. When they cannot be avoided, explain what the terms mean in simple language;
 - repeating important points in different ways;
 - summarising the key points.
6. Patients must be encouraged to ask questions about the research. Time must be set aside for the investigator to go over the information with patients to ensure that they understand all the implications. Patients will often only remember important questions after the first counselling. Provisions should be made, therefore, for follow-up visits if required.
7. The advice contained in this guidance covers three aspects of preparing information leaflets:
 - The information to be included
 - How to present the information
 - How to evaluate its effectiveness

What to include and how to structure the leaflet

8. A synopsis for the trial is useful (3/4 of a page).

9. An introductory paragraph may be helpful, explaining that the patient is being asked to take part in a research study. The following is a suitable example:

'You are being invited to take part in a research study. Before you decide whether to participate it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.'

Thank you for reading this.'

10. It is important to anticipate common concerns. Below are listed some common questions.

- Why have I been invited to take part in the study?
- Is the treatment really likely to help me or be of help to others? The answer should be unambiguous. There should be no false hope.
- Are there any risks or disadvantages for me?
- What will the treatment entail? How, when, where and how often will it be administered and monitored?
- What will the side effects be? Will it be painful or uncomfortable?
- What costs or inconveniences may I incur?
- What are the responsibilities placed upon me for follow-up?
- What will the trial help to demonstrate?
- What action should be taken if I become unwell?
- Who can I talk to about this study?
- How will the information obtained from this trial be used?
- How will my tissue samples being used?

11. The following points should be covered in addressing these concerns:

Why the research programme is being undertaken

Explain the purpose of the study. This needs to cover:

- (a) The research questions being asked:
- Why are they important?
 - How might they be answered?
 - Why has gene manipulation been chosen?
 - How the study has been designed:
 - Increasing dosage. Why is this necessary?

- Use of placebo controls and what this means.
- Does the study involve more than one centre?
- Evaluation of results.

(b) The implications of the research for the individual.

12. The following definitions may help explaining certain research methods:

Randomised Trial: Sometimes because we do not know which way of treating patients is best, we need to make comparisons. People will be put into groups and then compared. The groups are selected by a computer which has no information about the individual – i.e. by chance. Patients in each group then have a different treatment and these are compared.

You should tell the patients what chance they have of getting the study drug/treatment, for example, a one in four chance. Avoid percentages.

Blind trial: In a blind trial you will not know which treatment group you are in. If the trial is a double blind trial, neither you nor your doctor will know in which treatment group you are (although, if your doctor needs to find out he/she can do so).

Cross-over trial: In a cross-over trial the groups each have the different treatments in turn. There may be a break between treatments so that the first drugs are cleared from your body before you start the new treatment.

Placebo: A placebo is a dummy treatment such as a pill which looks like the real thing but is not. It contains no active ingredient.

Further definitions, for example, to explain phase I, II or III clinical trials are given the glossary.

Research procedures

13. Describe and explain the procedure(s) and commitment of participants in terms of time, costs, and how data will be collected (such as blood tests, x-rays, interviews). Describe any restrictions the research might place on the patient, particularly the use of isolation rooms and restrictions on visiting.

Consequences of participating

14. The predictable consequences of participating in the study should be explained.

- State whether or not there are possible benefits of participating in the proposed study. For research trials which are not reasonably expected to provide a therapeutic benefit to participating patients the information leaflet should clearly state that no direct clinical benefit is expected to occur as a result of participation in the study, although knowledge may be gained that may benefit others.

- Describe the nature and likelihood of risks, pain, injury or other harm, that may occur.
- Where it is appropriate to the patient, describe alternative therapies, including those being assessed in other research trials.

Non-participation or withdrawal from the study

15. Emphasise that participation in any study is voluntary. The decision to take part or not, should not influence any present or future treatment or care. Patients should know that they can withdraw from the study at any time without having to give a reason for doing so. Draw attention to any additional risks that might be associated with an incomplete course of treatment.

You could use the following paragraph:

'It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.'

Use of contraception

16. It is important to avoid the possibility that gene transfer could harm a fetus. Advise women that they should not become pregnant before or during the course of their participation in the study. Inform both men and women when effective contraception or abstinence is required during the active phase of their participation in the study and also for at least 3 months afterwards. Depending upon the nature of the research trial the information sheet might advise any woman not to participate if she thinks she may wish to become pregnant.

Confidentiality/ Privacy

17. Affirm that confidentiality of personal information of trial participants will be protected. State who might have access to their anonymised research records and why this is necessary. In trials where personalised data needs to be reviewed, the patient's agreement must be obtained and this aspect of the research should be clearly explored in the information leaflet.
18. A suggested form of words for drug company sponsored research is:

'If you consent to take part in the research any of your medical records may be inspected by the company sponsoring (and/or the company organising) the research for purposes of analysing the results. They may also be looked at by people from the company and from regulatory authorities to check that the study is being carried out correctly. Your name, however, will not be disclosed outside the hospital/GP surgery.'

19. A suggested form of words for all other research is:

‘All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it.’

Long term follow-up

20. It is important to evaluate the long term safety and efficacy of gene transfer. This requires co-operation of participants in follow-up beyond the active phase of the study. Explain the need for this commitment from the outset. The information leaflet or consent form should include a list of persons who can be contacted during the follow-up period.
21. Patients participating in gene therapy studies will be subject to clinical audit via the NHS central records system. In addition they will be invited to participate in the GTAC Flagging Project involving the NHS Central Registry and the Office of National Statistics. Proposers are asked to seek informed consent from all subjects at the time of their enrolment for monitoring of their long-term health and on behalf of any children that the patient may conceive following participation in the study.
22. The following paragraphs should be inserted into the patient information leaflet:

‘Gene Therapy is a new development. Every effort is made to be sure it is safe but we need to watch out for any unexpected effects. To make this possible, all people who have gene therapy are flagged by the NHS records system. Accordingly, your NHS number and details of the trial in which you are participating will be provided to the Department of Health (DH) so that your participation in this trial can be recorded on the National Health Service Central Register. This information will be used for purposes of long-term follow-up. You will not be contacted by DH directly but your GP may be asked to provide information on your health on occasion.

In theory, gene therapy could affect the next generation. To cover this possibility, any children born to a person who had gene therapy will be flagged also and followed through until they are 16 years old. This system is subject to the same protection of confidentiality as all medical records. Any studies of these medical records will be under the supervision of the Gene Therapy Advisory Committee of the Department of Health who will make sure confidentiality is respected.’

An additional sentence may be added to make clear to patients that participation is voluntary and there will be a separate information sheet and consent form for long term follow-up. Whether or not patients consent to take part in the Flagging Project should not affect their eligibility to take part in the trial.

Further support

23. The information leaflet should make clear to potential participants who can be approached for:
 - a. further information
 - b. independent counselling.

It might be helpful to make potential trial participants aware of a leaflet entitled 'Medical Research and You', published by Consumers for Ethics in Research (CERES). This leaflet gives more information about medical research and looks at questions potential recruits into clinical trials may want to ask. Copies can be obtained from CERES, PO Box 1365, London N16 0BW.

Evaluation of a Patient Information Leaflet

24. To determine how well an information leaflet will be understood it needs to be evaluated. Asking people not acquainted with the area to read the leaflet is the best way. They might include administrative or clerical staff in the hospital, or non-medical friends. The management of your hospital may be able to assist in "piloting" the leaflet. Patient groups and other voluntary organisations are an important source of advice on both design and piloting leaflets. The patient information leaflet should be no more difficult to read than typical text in the popular press.
25. Assessments of leaflets by patients might include measures of understanding and satisfaction with the information provided.

Special Issues

26. Potential trial participants need time to make a decision about their participation in the research. They should have an opportunity to consider the information provided, seek further information and to consult with a named independent counsellor.
27. Where the study involves children who are not capable of giving lawful consent, an information sheet for parents or guardians should be prepared according to the principles above. In addition, materials and explanations should be provided in accordance with the child's level of understanding (illustrated information leaflets and other material may be particularly useful). There will probably need to be different information leaflets where different age groups of children are prospective research subjects. As a matter of good practice, the child's assent to the research should be sought, and the informing process for obtaining assent mirrors that for consent.
28. There are special issues for adults who are not able to give informed consent by reason of mental incapacity. Researchers are advised to consult the section on "consent" in GTAC's standard operating procedures for details.
29. Additional consideration should be given to the needs and requirements of subjects whose first language is not English. The importance of written information is often

greater in such circumstances. Special care should be taken to have information leaflets in other languages checked for accuracy, and to ensure cultural and ethnic sensitivities are properly handled.

30. Every effort should also be made to ensure that individuals who have difficulty reading are not disadvantaged through lack of information.

A final checklist

31. The following check list may be useful in ensuring that all relevant information for trial participants is included. Have you included information about the following?

- ✓ Study title
- ✓ Invitation paragraph
- ✓ What is the purpose of the study?
- ✓ Why have I been invited to take part?
- ✓ Do I have to take part?
- ✓ What will happen to me if I take part?
- ✓ What do I have to do?
- ✓ What is the drug or procedure that is being tested?
- ✓ What are the alternatives for diagnosis or treatment?
- ✓ What are the side effects of any treatment received when taking part? (GTAC considers that this issue is often neglected in current PILs)
- ✓ What are the possible disadvantages and risks of taking part
- ✓ What are the possible benefits of taking part?
- ✓ What if new information becomes available?
- ✓ What happens when the research study stops?
- ✓ What if something unexpected happens or goes wrong?
- ✓ Will my taking part in this study be kept confidential?
- ✓ What will happen to the results of the research study?
- ✓ Who is organising and funding the research?
- ✓ Who has reviewed the study?
- ✓ Contact for Further Information

32. Patients should be given a copy of the patient information sheet and consent form to take away with them.

Suggested stock phrases

33. Where there are Association of the British Pharmaceutical Industry or other no-fault compensation arrangements the following (or similar) should be included (for example in the section “What if something unexpected happens or goes wrong”):

‘Compensation for any injury caused by taking part in this study will be in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI). Broadly speaking the ABPI guidelines recommend that ‘the sponsor’, without legal commitment, should compensate you without you having to prove that it is at fault. This applies in cases where it is likely that such injury results from giving any new drug or any other procedure carried out in accordance with the protocol for the study. ‘The sponsor’ will not compensate you where such

injury results from any procedure carried out which is not in accordance with the protocol for the study. Your right at law to claim compensation for injury where you can prove negligence is not affected. Copies of these guidelines are available on request from your study doctor.'

34. Where there are no Association of the British Pharmaceutical Industry or other no-fault compensation arrangements the following (or similar) should be said:

'If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to carry the legal costs. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.'

35. Tissue donation (for consent form)

"I confirm that I am content to donate samples from [insert, for example blood] taken during the study to be retained as an unconditional gift to research which has been approved by a Research Ethics Committee."

Glossary: please see Annex A of this report.

SECTION 5: GTAC PUBLIC MEETING DECODING CHILDHOOD GENE THERAPY

The 2004 GTAC public meeting focussed on childhood gene therapy and, judging by the feedback received, was one of the most successful GTAC public meetings to date. The full delegate pack of the meeting is available on the GTAC website (<http://www.advisorybodies.doh.gov.uk/genetics/gtac/publications.htm>).

5.1 SUMMARY

Professor Norman Nevin OBE, Chair of GTAC, opened the day by giving a summary of the progress of gene therapy for single gene disorders over the past decade as well as an account of clinical gene therapy trials in the UK with a view to the future of this technology.

Dr Bobby Gaspar spoke about one of the most successful gene therapy trials in the UK, the trials for X-linked severe combined immunodeficiency (SCID-X1). So far, seven children with SCID-X1 have been enrolled into the trial and Dr Gaspar spoke about encouraging results.

Professor Robin Ali was one of the successful winners of the Government's White Paper commitment for gene therapy single gene disorders (see also Section 7). Professor Ali spoke about the background to his proposed clinical trial for childhood retinal disease.

Professor Francesco Muntoni, who spoke on behalf of the UK Consortium of Duchenne Muscular Dystrophy, another winner of support from the White Paper for gene therapy single gene disorders. He outlined the background to the consortium's proposed trial of using a gene molecular patch to re-establish the function of dystrophin gene.

Mr Nick Catlin of Parent Project UK and **Mr Michael Moorwood** rounded off the session on muscular dystrophy by speaking about their respective experiences of the disease.

Dr Fiona Stewart spoke about the ethics of research in children and the principles governing this area. All research in children must have direct benefits for either the child themselves or for child health.

Finally, **Revd Dr Lee Rayfield**, spoke about the issue of public opinion of the technology and how accusations that scientists are 'playing God' may best be, and are being, addressed.

5.2 *What the audience thought of the public meeting*

Feedback forms were received from 62 members, 70% of the audience, who gave the following responses. 44% of responders classified themselves as scientists, 8% as students, and 48% as "other". "Others" who provided an explanation included nurse (5), parents of children with single gene disorder (4), genetic counsellor (4), charity representative (3), clinician (2), clinical genetics staff, doctor, health care professional, occupational therapist, MREC lay member, LREC member, science communicator, paediatrician, funding body member, interested non academic, and curious member of the public.

100% of delegates rated the event as Excellent (69%) or Good (31%). Everyone thought that the Government should continue to support UK gene therapy and clinical trials. 90% had discussed gene therapy with family and friends. Only 37% thought the event had changed their perception of gene therapy. 73% of delegates had heard of GTAC before attending the meeting.

There were a number of comments about whether the event had changed the delegate's perception of gene therapy. Below are some examples of comments:

- [No]. I feel without GT a cure will not be found for these single gene disorders.
- [Yes]. Understanding how gene therapy can be applied to a range of diseases.
- [Yes]. Helped me to better appreciate [more widely parental and patient perspectives and to be more aware of my own “patronising” bias.
- [No]. It has helped better educate me on the subject; my perception remains positive.
- [Yes]. I am less suspicious and am in a position to inform my LREC from a much firmer base.
- [Yes]. Very accessible and a nice mix of perspective/topics. Was impressed by the lack of “hyperbole” on part of scientific speakers.
- [Yes]. Despite working within the field, it is easy to become discouraged by the rate of progress. This day has provided me with an injection of motivation. Thank you.
- [No]. To rate the significance of disability is controversial. We can recognise muscular dystrophy by sight, but not colour-blindness. Gene therapy for both would improve their QOL. Both are curable by GT.
- [Yes]. Deeper understanding. Increased appreciation of research being done, and of wider issues.
- [No]. I support all advances which may lead to improvement in the quality of life.
- [Yes]. I am so surprised that gene therapy for children made so great development and is being real medical cure, which I have never heard in Japan.
- [No]. The talks by Michael Morwood and Nick Catlin were most invigorating to me as a researcher in DMD.
- [Yes]. The patients' participation has helped me realise many of gene therapy's implications.

And also many additional comments, particularly on issues to do with childhood gene therapy:

- Gene therapy is another method of treatment which we must explore. If it is potentially able to treat/ameliorate conditions which are up to now incurable or debilitating, we must support the clinical trials.
- Informed consent and adequate information giving to parents with particular emphasis on the psychosocial aspects of genetic research

- If my son can benefit from GT and there is a low risk/side effect balance, then it is something I shall look forward to.
- In terms of therapy, treatment or cure for children with life threatening conditions: 1) How [much] can public funding do? 2) At what point will the State (and public) ask what the overall benefits and costs to society are? 3) Who should decide whether or not a child can consent for themselves – in what circumstances and why?
- It was good to see that the researchers who are involved in this research are very aware of the limitations and ethical considerations of their work. It reassured me as to the image of the genetic scientist who is so involved in propagating his work that he has lost sight of the big picture.
- It was interesting to hear the perspectives of the patients and their families. It would also be interesting to hear what the general public thinks of these issues. Also – all the speakers were very clear and well chosen.
- Having a parent presentation on prospect of gene therapy and involvement in clinical trials was excellent and also a necessity for a holistic, patient/family focussed view. Is it possible to have feedback of families already treated?
- I liked the concept of the speakers of developing ways to cure a genetic disease, keeping a balance between theory (research work) and practice (knowing and working closely with patients!)
- We should have the vision to move the techniques forward and recognises that acceptable risks can be taken because no advance is possible without some degree of risk. This is not to say that risk should not be minimised by a proper approach.
- In some instances the limitations on research on children is an impediment to research – this must be balanced against the risk as an ethical issue.
- There is a fear of supporting viral vector research, and a move in future to non-viral options; success with, and the requirements for viral vectors needs to be promoted to the basic scientists.

5.3 SPEAKERS' BIOGRAPHIES

Biographies of the eight speakers, Professor Norman C Nevin OBE (GTAC Chairman), Dr Bobby Gaspar (Institute of Child Health & Great Ormond Street NHS Trust, London), Professor Robin R Ali (Institute of Ophthalmology & Institute of Child Health, London), Professor Francesco Muntoni (Imperial College London), Mr Michael Moorwood, Mr Nick Catlin, Dr Fiona Stewart (Belfast City Hospital) and Revd Dr Lee Rayfield (GTAC Member) can be found on the GTAC website (<http://www.advisorybodies.doh.gov.uk/genetics/gtac/publications.htm>).

5.4 PRESENTATIONS

Opening remarks

Professor Norman Nevin OBE Chair of GTAC

Almost 6000 disorders and traits have a single gene mode of inheritance. These conditions are due either to a mutated gene on an autosome (autosomal inheritance) or on an X-chromosome (X-linked inheritance). Several important and serious childhood diseases, such as cystic fibrosis, Duchenne muscular dystrophy, severe combined immunodeficiency (SCID) and some forms of childhood blindness, have typical Mendelian patterns of single gene inheritance.

The past decade has witnessed the elucidation of the human genome which has led to an increasing understanding of the molecular basis of disease; this has resulted in more accurate diagnosis and prognosis of single gene disorders and in novel therapeutic regimes, such as gene therapy and molecular vaccines.

Gene therapy is the deliberate introduction of a gene(s) or small DNA or RNA molecules to somatic cells and organs to correct a specific genetic defect. In the UK 1993-2003 a total of 94 gene therapy trials were approved by the Gene Therapy Advisory Committee (GTAC). The majority (74%) of trials involved the use of gene therapy in the management of cancer, whereas only 14% (n=12) were directed towards single gene disorders. In 2000, a landmark report by Cavazzano-Calvo et al of successful gene therapy in infants with X-linked SCID, indicated that the potential of gene therapy was achievable.

In June 2003, the Department of Health produced a White Paper entitled “Our Inheritance, Our Future: Realising the potential of genetics in the National Health Service.” The White Paper argues that although there has been some success in treating single gene disorders, much gene therapy research is unattractive to industry because of the small numbers of patients involved. To address this situation the Department of Health has made funding available to support gene therapy research into single gene disorders, to provide access to high standard vector production facilities and to examine safety issues.

Despite the ups and downs of gene therapy, today’s meeting will illustrate the ever increasing approaches for the application of gene therapy in single gene disorders in childhood. The logic behind gene therapy is compelling and everything we know about molecular biology tells us that it will work.

Balancing risk and benefit – the UK X-SCID story

Dr Bobby Gaspar, Institute of Child Health and Great Ormond Street NHS Trust

H Bobby Gaspar, Kathryn L Parsley, Steven Howe, Doug King, Kimberly C Gilmour, Joanna Sinclair, Gaby Brouns, Manfred Schmidt, Christof Von Kalle, Torben Barington, Marianne A Jakobsen, Hans O Christensen, Abdulaziz AlGhonaum, Harry N White, John L Smith, Roland J Levinsky, Robin R Ali, Christine Kinnon, Adrian J Thrasher

Background: X-linked severe combined immunodeficiency (SCID-X1) is caused by mutations in the common gamma chain (γ C), resulting in disruption of T lymphocyte and natural killer

(NK) cell development. B lymphocyte function is also intrinsically compromised. Allogeneic bone marrow transplantation is very successful if HLA-matched family donors are available, but HLA-mismatched procedures are associated with significant morbidity and mortality. We have investigated the application of somatic gene therapy for treatment of this disease.

Methods: Seven children with SCID-X1 who lacked good bone marrow donors have so far been enrolled into the study. Autologous bone marrow stem cells were corrected by gene transfer using a retroviral vector encoding the γ_c gene, and returned to patients without preceding chemotherapy conditioning. Patients were monitored for integration and expression of the γ_c vector, and for analysis of functional immunological recovery.

Results: All patients have shown major improvements in clinical and immunological parameters, and two of these patients are free from prophylactic medication. No serious adverse events have been recorded. In 5 patients T cells have responded normally to mitogenic and antigenic stimuli, and their T cell receptor (TCR) repertoire was highly diverse. Where evaluable, humoral immunity was also restored in terms of antibody production, and associated with increasing immunoglobulin gene somatic mutation rates.

Summary: Gene therapy for SCID-X1 is a highly effective strategy for restoration of functional cellular and humoral immunity. In view of serious adverse events in another SCID-X1 study in Paris, the use of gene therapy must be based on careful assessment of risks and benefit and decisions made in close consultation with parents.

Gene therapy for eye disease

Professor Robin R Ali, Institute of Ophthalmology & Institute of Child Health, University College London

The eye is one of the best targets for gene therapy because, compared to other tissues, the eye is easily accessible and may allow localised exposure of the target tissue to therapeutic agents with reduced risk of systemic effects. Furthermore, the effects of treatments may be monitored by a variety of non-invasive examinations. There are many ocular disorders (caused by single gene defects as well as those of complex etiology) which may be amenable to gene therapy. Whilst the most obvious application of gene therapy is for treatment of recessive single gene disorders by the introduction of a missing gene product, there is also the possibility of treating dominant disorders by the introduction of genes encoding siRNAs which reduce the level of abnormal gene product. An alternative strategy is the introduction of genes whose products may ameliorate the disease process without correcting the underlying genetic defect. In the case of complex or multi-factorial diseases this is currently the only possible approach.

Over the past five years there has been considerable progress in developing gene therapy for ocular disease. Retinal disease is the primary focus for much of the work that is being carried out. This is partly because of the lack of effective treatments, but also due to the identification of a large number of single gene defects that give rise to retinal degeneration, and because of the existence of a number of well-characterised animal models that may be used to develop therapeutic protocols. Furthermore, there are few other diseases in which preservation of just a few thousand cells might result in significant functional consequences to the patient. To provide some indication of the prospects for effective application of this

technology for the treatment of eye disease, I shall provide examples of pre-clinical studies using a variety of animal models.

Bypassing the genetic defect in muscular dystrophy

Professor Francesco Muntoni, Professor of Paediatric Neurology, Imperial College London

On behalf of the UK Consortium of Antisense Oligonucleotides in Duchenne Muscular Dystrophy (Prof. Francesco Muntoni, London; Prof. Kate Bushby, Newcastle; Prof. Terry Partridge, London; Dr Qi Lu, London; Dr Dominic Wells, London, Dr Matthew Wood, Oxford; Prof George Dickson, London). Supporting charities: Muscular Dystrophy Campaign (Jenny Versnel, project coordinator); Duchenne Family Support group; Parent Project UK.

Duchenne muscular dystrophy is a common genetic disease, affecting one boy every 3.500 newborn males, for which there is currently no cure. It is a severely progressive condition: affected children are diagnosed in the first few years of life, lose the ability to walk by the age of 12 and develop cardiac and respiratory failure in the late teens. Without cardio-respiratory intervention, affected individuals do not survive beyond the late teens.

The condition is due to a genetic defect, typically the missing (deletion) of one or more exons in the dystrophin gene, located on chromosome X. The large size of this gene has hampered attempts to replace it using conventional gene therapy approaches.

More recently, significant progress has occurred in exploiting an alternative technique, the delivery of antisense oligonucleotide (AO) to correct the genetic defect in the dystrophic muscle lacking dystrophin. The mechanism of action of AO is to provide a 'bridge' between the two parts of the gene interrupted by the deletion. These AO therefore allow the production of a partially functional dystrophin. Experimental work performed in a spontaneous occurring mouse model of Duchenne muscular dystrophy, the mdx mice, have showed that the administration of these AO is capable of restoring the production of a partially functional dystrophin. This molecule is sufficiently good to protect the muscle from the progressive degeneration that characterise the condition.

The current DH trial is aimed at using direct muscle injection of these molecular patches to restore the production of dystrophin in individuals with Duchenne muscular dystrophy. Parallel preclinical studies will be performed to optimise the chemical modification of the AO so that they are more stable; and to identify modalities to administer them systemically, in order to avoid, in the future, the need for the direct muscle injection.

One Giant Leap

Mr Nick Catlin

On this day in 1969 Neil Armstrong summed up the pinnacle of Space Age travel "That's one small step for man, one Giant leap for mankind" .when he stepped onto the moon. Can the genetic revolution of the 21st Century offer similar scientific achievements and hope for children suffering from fatal genetic conditions like Duchenne Muscular Dystrophy?

Counselling and consenting children

Dr Fiona Stewart, Belfast City Hospital

Research in children has always been a controversial area. After the second world war it was banned until the declaration of Helsinki in 1964. However research in children is vital if we are ever to try and optimise treatment for diseases of childhood. It is important that we appreciate that children are not ‘little adults’. They have their own particular needs and research involving children needs to take these needs into consideration.

Research in children must involve co-operation between researchers, clinicians, families and the children themselves where possible. All research in children must have direct benefits for either the child themselves or for child health in children. The potential benefits of any research must be clearly seen to out-weigh any potential harm to the child.

Children are in a unique position in that they are in the only group of people for whom someone else can give consent. Researchers must assess whether the child is able to freely give informed consent or whether consent should be sought from parents. In all cases it is important to give adequate information in an understandable format to allow the child or the family to give fully informed consent. This may require some imagination on the part of the researchers and always a considerable amount of time. The child’s interests must always come first and refusal of the child to participate should be respected. Likewise signs of acute distress in the child should be accepted as a refusal and also respected. Ethics committees exist to ensure that research is justifiable and is being conducted in an ethically acceptable manner. It is however important that there are individuals on these committees with sufficient expertise in dealing with children to enable these committees to give appropriate advice.

Gene therapy: Playing God?

Revd Dr Lee Rayfield, GTAC Member

For a large number of people manipulating the genome is equated with ‘playing God!’ Many have an instinctively negative reaction, reinforced by media headlines stressing potential hazards and threats. Although Gene Therapy may be perceived more favourably than crop modification there is still significant public unease. This needs to be recognised and adequately addressed by those in the field and by Government.

‘Playing God’ is effectively a catch-all phrase covering a variety of concerns, not all of which relate to theological conviction. DNA is accorded a quasi-religious status, there are fears of biological catastrophe and anxieties about where Gene Therapy will lead us. The complexity of the technology and feelings of powerlessness and suspicion contribute to the accusation that scientists are ‘playing God’. All of these need to be taken seriously. That said, reflections on the nature of God and humanity from a Christian perspective affirm the responsible development of Gene Therapy.

The current oversight of GTAC and other regulatory agencies provides for a ‘critical friendship’, with opportunities and constraints that are consistent with Christian understanding. Rather than ‘playing God’, with appropriate safeguards Gene Therapy represents an authentic expression of ‘being human’ which can be commended.

SECTION 6: UPDATE OF CLOSED UK CLINICAL TRIALS

The following are short summaries provided by researchers of closed gene therapy trials. GTAC would like to thank all researchers who have contributed to this section. The summaries are essentially unedited and reflect the views of the researchers.

6.1 CANCER GENE THERAPY TRIALS

6.1.1 Ovarian Cancer

GTAC 14B: Phase I, open-label, dose-escalation trial of intraperitoneal injection with an E1B attenuated adenovirus in patients with recurrent/refractory ovarian carcinomas

Lessons learnt from this trial were that intra-peritoneal administration of genetically modified material, including adenovirus, can be problematic – particularly when the abdomen contains bulky intra-peritoneal tumours. Best results may be obtained when the peritoneal cavity contains only small volume disease. Recovery of tumour cells from peritoneal washings, for biological studies, can also be problematic. As a result, it was not possible to conclude whether or not the adenovirus was capable of replicating in tumour cells *in vivo*. (Vasey *et al*, 2002, *J Clin Oncol* 20(6):1562-9)

GTAC 022: A multiple ascending dose study evaluating the safety and the gene transduction into malignant cells after the administration of E1A-lipid complex by intra-peritoneal administration in patients with epithelial ovarian cancer who over express HER-2/neu

The active ingredient of this phase I trial was E1A Plasmid DNA formulated with a lipid carrier comprising of DC-Chol B:DOPE at a ratio of 3:2. In this open-label, non-randomised, multicentre study, successive cohorts of at least 3 patients with Grade III/IV ovarian cancer showing overexpression of the HER-2/neu gene received ascending doses of the E1A-lipid complex. This was administered by peritoneal infusion during a maximum of 6 courses of therapy (one administration per week for three weeks and one week of rest) into the peritoneal cavity. The progression of doses from one dose level to the next was based on review of the drug related toxicity. Biological responses were evaluated primarily from changes in E1A gene transfer and HER-2/neu down-regulation. Tumour responses (number and size of tumours as measured by CT scanning) were used as secondary criteria of efficacy. It was intended that all patients would continue to participate in a long-term 5-year follow-up every 2-4 months for the first 6 months, then once a year indefinitely. Number of patients: fifteen (14 eligible for dose-escalation analysis).

RESULTS:

Safety

- E1A/lipid complex administered by intraperitoneal infusion was well tolerated at 1.8 mg DNA/m²

- Dose dependent abdominal pain was observed at the higher doses tested (3.6 and 7.2 mg DNA/m²)
- A pre-treatment regime demonstrated that the abdominal pain could be managed
- The adverse event profile was dominated by the underlying disease

Efficacy

- EIA gene transfer and expression in tumour cells were observed in all patients
- Down regulation of HER2/neu overexpression was observed in one patient.
- The clinical outcomes were typical of the underlying disease

CONCLUSIONS: The study achieved its primary end points of safety and tolerability, EIA gene transfer and expression. No conclusion may be made regarding efficacy or clinical proof of principle from this study. Monotherapy with EIA/lipid complex would not seem appropriate in this late stage disease, high tumour burden patient population.

GTAC 030: Use of a retrovirus carrying human cytochrome p450 for the treatment of ovarian cancer (phase I intra-abdominal)

PRIMARY OBJECTIVES

1. To assess the safety of ascending doses of MetXia-P450 alone or in combination with carboplatin or carboplatin/cyclophosphamide.
2. To assess gene transfer efficiency into intraperitoneal tumour nodules and normal peritoneal tissues when MetXia-P450 is given by intraperitoneal injection.
3. To assess the gene expression efficiency of *lacZ* marker and cytochrome P450 2B6 genes in intraperitoneal tumour nodules and normal peritoneal tissues.
4. To assess biodistribution of the vector and gene products in the blood.
5. To assess the immunological response to vector components and transgenes.

SECONDARY OBJECTIVE

To assess the CA125 response of tumours to treatment with MetXia-P450 in combination with administration of intravenous carboplatin or oral cyclophosphamide and intravenous carboplatin.

SUMMARY

Intraperitoneal MetXia-P450 was generally well tolerated. The most common treatment related adverse event was abdominal pain, which occurred in three of six patients. Gene transfer was detected, by histochemistry, in biopsy samples in only one of three patients tested, all of whom received MetXia-P450 10x. As a result, samples from the patients in the lower strength group were not assayed and PCR-based assays to detect transduction were not performed. Vector egress from the site of injection was detected by P450 RT-PCR at both 1 and 4 hours after injection in two patients receiving MetXia-P450 1x and in three receiving MetXia-P450 10x. No free vector was detected at 24 hours post-injection. Vector

integrated into peripheral blood mononuclear cells (PBMC) was detected by P450 PCR at Week 12 in two patients receiving MetXia-P450 1x and at Week 1 in one patient receiving MetXia-P450 10x. However, integrated vector was not detected by gag P30 PCR. Antibodies against gag P30 were detected in all six patients at Week 3 and Week 12; antibody was not found before injection. In the light of the low rate of gene transfer at the higher strength, the study was stopped prematurely. Conversion of the prodrug (cyclophosphamide) was predicted to be negligible and it was considered unethical to proceed.

6.1.2 VULVAL, CERVICAL AND ANO-GENITAL CANCERS

GTAC 012: Use of a recombinant vaccinia virus for therapy of cervical cancer

GTAC 012A and 012B: Use of a recombinant vaccinia vaccine (TA-HPV) to treat cervical intraepithelial neoplasia III

Vaccinia virus has been widely used as an immunogen and was well tolerated. It has been accepted as safe when it was used during the smallpox eradication program of the WHO. In addition, vaccinia induces a strong immune response by itself that may deliver “danger signals” for the immune system that represent an adjuvant effect. Therefore, based on the Wyeth vaccinia strain, a recombinant virus was constructed carrying functionally modified E6 and E7 genes of HPV-16 and -18. During the lytic life cycle of the virus, the inserted HPV genes are expressed, and their proteins are processed and presented by antigen-presenting cells to induce a MHC class I-restricted T-cell response. In women with advanced cervical cancer, a single treatment with this modified vaccinia virus produced HPV-specific cytotoxic T lymphocytes (CTLs) in one of three patients and a HPV-specific antibody response in three of eight patients (Borysiewicz *et al*, 1996, *Lancet* 347:1498).

The GTAC 012 series of trials covered the use of the same construct, called TA-HPV, in patients with early-stage cervical cancer. One part of the rationale in this trial was that these patients were less likely to have compromised immunity than those with advanced cancer thereby potentially improving the response rate to the vaccine and any clinical efficacy. A study was conducted to assess the safety and immunological effects of vaccination with TA-HPV. Twenty-nine patients with clinical International Federation of Gynecologists and Obstetricians (FIGO) stage Ib or IIa cervical cancer were given two vaccinations with TA-HPV at least 4 weeks apart, starting 2 weeks before radical hysterectomy. Patients were monitored closely for side effects of the vaccination. Serial blood samples were examined for HPV-specific CTLs or changes in levels of antibodies to HPV-16 or -18 E6 and E7 proteins and to vaccinia virus.

Vaccination with recombinant vaccinia was well tolerated in all patients with only mild to moderate local toxicity, and no serious adverse events were attributable to the vaccine. After a single vaccination, HPV-specific CTLs were found in four patients (HLA A1, A3, three patients; HLA A1, A24, one patient). Eight patients developed HPV specific serological responses. This study confirmed the safety and immunogenicity of the vaccine in a proportion of those patients vaccinated. However, the down-regulation of MHC class I molecules in the tumor in many cases of cervical cancer could mitigate against an anti-tumor effect of the CTLs *in vivo*. To date, 26 patients are on study for 5 years of follow-up. This number is much too small for any prospective evaluation on tumor recurrence or

metastasis. In the patients in whom HPV-specific CTLs were detected after vaccination with TA-HPV, the responses appeared to be transient. This could be due to homing of lymphocytes out of the peripheral blood or may indicate that the immunogenicity of the vaccine needs to be enhanced. (Kaufmann *et al*, 2002, *Clinical Cancer Research* 8:3676-85)

GTAC 012C: Use of recombinant vaccinia vaccine (TA-HPV) to treat vulval intraepithelial neoplasia III

This covered a study to evaluate the TA-HPV immunization regimen in patients with high-grade vulval intraepithelial neoplasia (VIN) since this may offer an opportunity to measure objective clinical responses as well as immunogenicity associated with the therapeutic HPV vaccination. VIN is a high-risk HPV-associated condition which has increased in incidence over the last 20 years, particularly in younger women. The multifocal presentation, high recurrence rate, and uncertain risk of progression to malignant disease makes VIN a difficult disease to treat. Intractable symptoms including itch, pain and psychosexual dysfunction are common and in the past many women have been subjected to repeated and disfiguring surgery in an attempt to control their disease.

Eighteen women with HPV-16 positive high-grade VIN were vaccinated with TA-HPV. The extent of their baseline disease was compared after 24 weeks by lesion measurements and histological analysis. Viral load was assessed pre- and post-vaccination by real time PCR. Cell-mediated immunity to HPV-16 E6 and/or E7 peptides (*HLA-A2* epitopes) or vaccinia-infected cell lysates was determined by IFN- γ enzyme-linked immunospot (ELISPOT) and T cell proliferation using an HPV 16 L2E6E7 fusion protein. Antibodies were measured by ELISA using vaccinia-infected cell lysates or HPV 16 and 18 E6 and E7 glutathione S-transferase-fusion proteins. Lesion-infiltrating CD4, CD8, CD1a, and CD68 immune cells were assessed by immunohistochemistry.

The single vaccination with TA-HPV was well tolerated, and all patients showed an increased ELISPOT and/or antibody response to vaccinia. There were significant differences in HPV-16 E7-specific ELISPOT and L2E6E7 proliferative responses in the patients at one or more time points post-vaccination as compared with the pre-vaccination status; two patients showed transient increased antibody responses. Overall, 13 women showed an increased HPV-16 specific immune response by one or more methodologies after immunization. Eight patients demonstrated a reduction in lesion diameter of at least 50% and a further four patients showed significant symptom relief. Viral load was reduced or cleared in six of eight lesion responders but also in six of ten non-responders. Before vaccination, clinical responders had significantly higher levels of lesion-associated CD4, CD8, and CD1a-immune cells than non-responders. There were no differences in CD68 (macrophages) between responders and non-responders before or after vaccination. Non-responders did show a significant increase in CD4- and CD8- but not CD1a-immune cells post-vaccination but at lower levels overall than responder patients. Local immune infiltration may be a critical factor in potential responsiveness to vaccine therapy in HPV-associated neoplasia and should be carefully monitored in future trials of immunotherapy for VIN.

This was the first demonstration of clinical and immunological responses after immunotherapy in women with HPV-16 associated high-grade VIN. Vaccination with TA-HPV was associated over the course of the study with objective clinical responses in 44% of

patients and symptom relief in a further 22%. Ultimately, to confirm the role of vaccination in these responses, it will be necessary to perform trials with random allocation of patients to both an immunotherapy group and a placebo group, possibly comparing vaccination with one or other method of conventional treatment. Whereas 12 women demonstrated a reduction in viral load after vaccination, only one patient showed complete viral clearance. Delivery of cure in this and other HPV-associated conditions, however, may depend on viral clearance or at least sustained anti-HPV immunity, and it is possible that a single vaccination is just not enough. This might be achieved by using a prime-heterologous boost immunization protocol. (Davidson *et al*, 2003, *Cancer Research* 63:6032-6041)

GTAC 012D: Use of a recombinant vaccinia vaccine (TA-HPV) to treat ano-genital intraepithelial neoplasia III

Here, twelve male and female patients received a single vaccination of TA-HPV with no serious adverse events reported. The AGIN lesions were assessed visually for signs of disease progression over a 24 week period following TA-HPV vaccination: These clinical observations were encouraging, with a single complete regression of AGIN lesions observed. Vaccine immunogenicity was confirmed by evidence of *de novo* or increased serological and/or cell mediated immunity to vaccinia virus. T-cells recognising HPV-16 E6 or E7 peptides or protein were detected in 8 patients pre- and post- vaccination. Six of the patients generated a new or boosted response following vaccination.

GTAC 059: 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)

Here, high grade VIN patients received three immunisations with the HPV-16 L2E6E7 fusion protein (TA-CIN) followed by a boost with TA-HPV. In preclinical studies, a heterologous prime-boost immunization strategy using TA-CIN, in combination with TA-HPV, showed enhanced immunogenicity compared with the use of either agent alone with the protocol of TA-CIN followed by TA-HPV superior to the reciprocal as defined by the induction of T-cell reactivity against the oncoproteins. Immunization with TA-CIN is thus likely to focus the immune response to the oncoproteins, whereas boosting with TA-HPV will increase the magnitude of this oncoprotein-specific T-cell response.

Twenty-nine women with high grade AGIN received three intramuscular doses of TA-CIN (HPV-16 L2/E6/E7 protein) at four weekly intervals followed by a single dermal scarification of vaccinia HPV-16/18 E6/E7 and were followed up for 12 weeks. Immunity to HPV-16 was assessed by lymphoproliferation, IFN- γ enzyme-linked immunospot (ELISPOT), and ELISA.

The patient group significantly responded to TA-CIN and not to the control antigen HPV-6 L2/E7 at all postvaccination time points when compared with baseline responses ($P < 0.05$). Ten of the patients showed at least a 3-fold increase in TA-CIN-specific proliferation at one or more time points after vaccination. Comparison of stimulation with HPV-16 E6- or E7-GST fusion proteins showed that proliferative responses were biased to HPV-16 E6. This bias was also seen by IFN- γ ELISPOT using overlapping peptides, with HPV-16 E6- or E7-specific T cells being detected in 9 and 2 patients, respectively. In addition, vaccination resulted in the induction of antibodies against the HPV-16 oncoproteins. Of the 6 clinical

responders, 2 patients showed both a proliferative TA-CIN-specific response and an E6-specific IFN- γ response, whereas 3 other patients displayed E6-specific reactivity only. Stable disease was recorded in 19 patients, 8 of whom showed a concomitant TA-CIN-specific proliferative and/or E6-specific T-cell response. Of the 4 progressors, 2 failed to make a T-cell response and 2 responded by either proliferation or E6 ELISPOT alone.

Interestingly, those patients with the lowest pre-existing TAC-IN specific response were most likely to respond vigorously upon vaccination with TA-CIN. This might be indicative of a pre-existing response masking vaccination induced changes, with respect to the quality or type of T-cell response, not measured by the proliferation assays. In some of the cases, a non-protective type of immunity (e.g., Th2, Treg, or non-polarized) pre-existing T-cell response may exist or the E6- and E7-specific T cells could have been anergized through the presentation of the two oncogenes to the immune system in a noninflammatory context. However, although priming of E6-specific T-cell reactivity is achieved by vaccination with TA-CIN, the major increase in E6-specific T-cell reactivity is due to the booster vaccination with TA-HPV. Such HPV-16 E6-specific T-cell immunity is frequently detected in healthy subjects, and this is supportive of a role in protection against persistent HPV infection and associated development of malignancies. The fact that the heterologous prime-boost protocol increases the numbers of these effectors should therefore offer potential therapeutic value in some of the high-grade VIN patients.

There is no statistically demonstrable association between clinical response and immunological response measured by either TA-CIN proliferation or ELISPOT or anti-E7 antibodies (odd ratios of 0.36, 0.11, and 0.16, respectively). However, such individual immune responses of patients were defined by 3-fold increases in activity from baseline and are thus a reflection of the magnitude of measurable vaccine induced change rather than inherent HPV immunity. Focusing on combinations of immunological activity, outcome of vaccination in patients and other factors may give another perspective. Our previous analysis of vaccinated VIN patients showed that clinical responsiveness to treatment was dependent on the presence of lesion-associated CD4, CD8, and CD1a immune cells, suggesting that not only the numbers of systemically present HPV-16-specific T cells are important but also their capacity to reach the target site. The patients treated in this study have premalignant HPV-associated lesions, which can show evidence of altered HLA class I expression, thereby facilitating immune escape from any CTL generated by the vaccination. In the design of new trials, local immune infiltration and HLA lesion expression will be important factors to consider in relation to outcome. Pre-selection of high-grade VIN patients with HLA class I-positive lesions displaying T-cell infiltrate before vaccination may identify a group of subjects who benefits the most from vaccination. (Smyth *et al*, 2004, *Clinical Cancer Research* 10:2954-296)

To describe the immunization regimen as prime-boost in this therapeutic approach to treatment of patients with lesions likely containing the HPV-16 proteins used in the vaccine formulations may not be entirely appropriate. The preference in the order of the immunisations derived from the animal models may not reflect the disease situation since the latter used HPV naïve mice. To see if there was any gross difference in outcome with the reciprocal order of TA-HPV and TA-CIN vaccination, 10 women with HPV 16-positive high grade VIN, previously primed with TA-HPV, received three booster immunisations with TA-CIN. All but one demonstrated HPV 16-specific proliferative T-cell and/or serological responses following vaccination. Three patients additionally showed lesion shrinkage or

symptom relief, but no direct correlation between clinical and immunological responses was seen. (Davidson *et al*, 2004 *Vaccine* 22:2722-2729)

SUMMARY

All of the above studies (GTAC 012 and 059) have crafted the future direction of clinical trials for HPV therapeutic vaccines to target local immunisation with a focus on activation of the innate immune response followed by immunisation with HPV oncogene vaccines in patients with high grade VIN. The primary endpoints will be clinical response and evaluation of local as well as systemic immune factors.

6.1.3 Colorectal cancer

GTAC 039: Gene therapy protocol for the evaluation of the safety, biodistribution and efficacy of TroVax in patients with metastatic colorectal cancer (Phase I i.m.)

PRIMARY OBJECTIVES

1. To assess the safety and immunogenicity of ascending doses of TroVax injected intramuscularly and intradermally.
2. To assess biodistribution of the vector and gene.

SECONDARY OBJECTIVE

To assess efficacy in a preliminary way in terms of effect on time to disease progression.

SUMMARY

TroVax appeared to be tolerated well, although locally occurring CTC grade I injection site erythema was more prevalent with intradermal dosing than intramuscular dosing. The analysis of immunological data indicated that TroVax given via either the intramuscular or intradermal route was able to induce humoral and cell-mediated responses to 5T4. The induction of an initial immune response to 5T4 could be seen within two weeks, but more usually occurred within six weeks for antibody and eight weeks for the T-cell response (when recombinant human 5T4 protein was used as the antigen in the assay). It appeared that the T-cell response was transient and in some patients could be boosted when additional doses of TroVax were given.

There did not appear to be a dose escalation effect between the three doses of TroVax when given via the intramuscular route using conventional needle delivery. However, it does appear that the higher dose (6.83×10^8 pfu [10x, i.m.] group) induced earlier initiation of a T-cell proliferation response. Additionally for this dose, all patients showed 5T4 antibody and cellular responses. The humoral response following intradermal injection was similar to that following intramuscular injection. The cell-mediated responses following intradermal injection were slightly delayed and weaker than those for the intramuscular injections, however, there was some evidence that they may have been less transient. Extensive tumour necrosis, from CT scan analysis, was observed in one patient at Week 20, which was coincidental with a 5T4 and T-cell response. Additionally, those patients with tumour assessments of 'No Change' showed both 5T4 antibody and T-cell responses.

Five patients showed periods of disease stabilisation and one patient, although they had progressive disease, did show evidence of tumour necrosis. The incidence of deaths, SAE and AEs that led to withdrawal is not unexpected in this patient population. There was no clinically significant difference between the treatment groups in the time to disease progression.

6.1.4 Breast cancer

GTAC 011: Genetic prodrug activation therapy for breast cancer: a phase I clinical trial of erbB-2-directed suicide gene expression

PURPOSE: This trial was designed to test the safety and efficacy of a tumour-specific genetic prodrug activation therapy targeted by use of the human erbB-2 gene promoter. The erbB-2 oncogene is overexpressed in approximately 20% of cases of breast cancer and is associated with poor prognosis.

PATIENTS AND THERAPEUTIC AGENT: Twelve breast cancer patients received transcriptionally targeted gene therapy in a phase I clinical trial using direct intratumoral injection of a plasmid construct combined with systemic administration of prodrug. The genetic prodrug activation therapy was specifically targeted to erbB-2-overexpressing breast cancer cells by use of a therapeutic cassette that contains the *Escherichia coli* cytosine deaminase gene driven by the tumour-specific erbB-2 promoter, thus allowing activation of fluorocytosine to the active cytotoxic fluorouracil only within tumour cells that express the oncogene.

RESULTS: The approach was shown to be safe and to result in targeted gene expression in up to 90% of cases. Using a number of different assays, it was demonstrated that significant levels of expression of the suicide gene were specifically restricted to erbB-2-positive tumour cells, confirming the selectivity of the approach.

CONCLUSION: The results of this study, the first targeted gene therapy for breast cancer and the first to use the cytosine deaminase system in human subjects, are encouraging for the development of genetic prodrug activation therapies that exploit the transcriptional profile of cancer cells.

GTAC 027: The use of MetXia-P450 for the treatment of advanced breast cancer (phase III intratumoral).

PRIMARY OBJECTIVES

1. To assess the safety of ascending doses of MetXia-OB80 injected into metastatic cutaneous tumour nodules.
2. To assess gene transfer efficiency in cutaneous tumour nodules.
3. To assess the gene expression efficiency of lacZ marker and cytochrome P450 2B6 genes in cutaneous tumour nodules.

4. To assess biodistribution of the vector, genes and gene products in cutaneous tumour nodules and in the blood.
5. To assess the immunological response to vector components and transgenes.

SECONDARY OBJECTIVES

1. To assess the macroscopic tumour response to treatment with MetXia-OB80 in combination with oral administration of cyclophosphamide.
2. To assess the histological and biochemical response of tumours to treatment with MetXia-OB80 in combination with oral administration of cyclophosphamide.

SUMMARY

The treatment regime of MetXia-OB80 and cyclophosphamide was well tolerated (up to a maximum dose of 5×10^7 Iu/0.5ml of tumour volume) by all 12 patients in the study. No significant toxicity was observed and of the total 196 adverse events that were reported, none were classified as definitely related to MetXia and only 13 were classified as being either probably or possibly related to MetXia. Gene transfer was detected, by two independent methods, in biopsy samples taken from patients in each of the three dose groups. However, the levels detected were modest and a clear correlation with the dose of MetXia-OB80 administered was not established. Two patients showed a partial response to treatment, with one showing improvement in an untreated as well as a treated lesion. The clinical improvements seen in both patients were associated with indications of an anti-tumour immune response and a reduction in the level of circulating surrogate markers for tumour burden, which suggest that administration of MetXia-OB80 to one tumour in a patient may elicit an anti-tumour immune response that can destroy other tumours in the same patient. As part of normal disease management, the progression of the principal metastatic tumour masses in each patient were monitored and this was recorded in the case report forms (CRFs). As expected for a trial of this type, none of the patients showed any indication of departure from the expected progression of their disease.

BC1 was a successful trial, with its primary objectives being met and the results contributing to its secondary objectives, passing pre-trial expectation. The data show that MetXia is worthy of further clinical development and to this end the follow-on product, MetXia-OB83, was tested in a second breast cancer trial (denoted BC2, GTAC 060).

GTAC 057: A phase I, multidose study to evaluate the safety of intramuscular injections of HER-2 DNA in patients with metastatic breast cancer.

Cancer cells have on their surface proteins that are not usually found on the surface of normal cells. In approximately 20-30% of women diagnosed with breast cancer, an overexpression of the Human Epidermal Growth Factor Receptor 2 (HER-2) is found. HER-2 DNA is a therapeutic DNA vaccine which encodes a modified HER-2 antigen. In animal models of HER-2 tolerance, immunisation with the HER-2 DNA induced HER-2 specific cytotoxic T-cells and modest antibody responses, resulting in significant, protective anti-tumour immunity. The trial aimed to evaluate short-term safety of intra muscular HER-2 DNA in patients with metastatic breast cancer whose tumours overexpress HER-2. The secondary objectives were to evaluate the ability of the vaccine to bypass tolerance for the

self-protein HER-2 by raising cellular and/or humoral immune responses and to assess the evidence of anti-tumour activity of the vaccine associated to such a response.

METHODS

27 women (age: 39-78 yrs) with HER-2 positive breast cancer were enrolled in an open label, multicenter, dose escalation Phase I trial. They received HER-2 DNA as intramuscular injections at three different dose levels (0.2 mg, 1.0 mg or 5.0 mg naked plasmid DNA). Each patient received a total of five immunisations with 2 weeks intervals followed by a 16 weeks follow-up period.

RESULTS

Of the total 27 patients recruited, 16 completed the planned five immunisations and 11 patients discontinued the study treatment prematurely because of progressive disease. Of the 16 patients who completed the full course of five vaccinations, three patients were followed-up until the final study visit, 16 weeks later. Ten patients were taken off study before due to progression of their disease, and two patients due to non-related serious adverse events. One patient is still on study.

Safety. Possible/probable related adverse events (n=12) were reported in 5 patients: pruritus (grade 1), pain in hip (grade 2), and lethargy (grade 1) reported twice, dermatitis (grade 1) reported twice, and pain at injection site (grade 1) reported 6 times. The events had no impact on study treatment and the patients recovered without sequelae. The reported injection site reactions were all grade 1 and short lasting (minutes). None of the SAEs (n=21) reported in 11 patients were related to study drug.

Immune response. Fourteen out of 27 patients had blood samples with sufficient numbers of PBMC isolated to allow the analysis of HER-2 specific T-cell reactivity by IFN-ELISPOT. All but one patient had samples eligible to analyse HER-2 specific IgG type antibody responses. Analysis of the T-cell reactivity revealed that only 4 patients responded at baseline as well as post-vaccination. After vaccination, five patients showed a HER-2 specific T-cell response. Four out of these 5 responses were detected after vaccination only. In 2 out of 4 patients, the baseline sample did not respond against the positive controls, and as such a negative response to HER-2 at baseline may be due to poor sample quality. Importantly, the two other patients displayed at both time-points a response to the positive controls but to HER-2 post-vaccination only, suggesting that at least these HER-2 specific T cell responses were induced by the vaccination and could be classified as definite T-cell responders. Antibody (Ab) responses: In 6 patients HER-2 specific IgG responses were detected, 3 of those were already present before vaccination. In two patients T-cell reactivity coincided with the presence of HER-2 antibodies. The patients with pre-existing antibodies had titres through the whole study period but without any significant increase as compared to baseline values.

Tumour response. Stable disease was confirmed in one patient at the second dose-level (1 mg) 169 days after the first immunisation, and this patient also had a definite immune response. The patient had multiple bone metastases at study entry. One patient had metastatic lesions in the liver with 6 target lesions as measured by CT-scan at study entry. At day 71 one of the target lesions had regressed (baseline: 16 mm; day 71: 9 mm) and the other 5 lesions were not measurable. This patient did not have blood samples analysable for T-cells, and did not have

any Ab response. The patient is still on study and will have a tumour assessment at the next scheduled visit day 120. Another patient with multiple lung, bone, and lymph node metastases and a solitary liver metastasis at entry had a supraclavicular lymphnode, which regressed from a baseline value of 50 mm to 15 mm at day 29. However, at day 43 the patient was taken off study due to progression of the visceral and bone disease. This patient had a definite T-cell response, no Ab response was detected. Finally, stable disease was recorded in a patient at the first dose-level (0.2 mg). The patient had multiple pleural metastases at baseline and was recorded as having stable disease at day 29. Progression was recorded at day 71. The patient had a definite immune response (T-cell and Ab).

CONCLUSION

Active immunotherapy with up to five repeated doses of HER-2 DNA is safe and well tolerated at all three dose levels investigated, and capable at activating HER-2 specific T cells and raising antibodies in patients with HER-2 positive metastatic breast cancer. Furthermore, there is evidence that the HER-2 DNA vaccine may exert anti-tumour activity in patients with breast cancer whose tumour overexpress the HER-2 receptor. The results from this trial supports subsequent clinical investigations of HER-2 DNA to further demonstrate the safety and the anti-tumour activity of the vaccine.

6.1.5 Melanoma

GTAC 06: The treatment of metastatic malignant melanoma with autologous melanoma cells that have been genetically engineered to secrete IL-2

It has been recognised for many years that melanoma is an immunogenic tumour and that tumour regressions can occur with immunotherapy. Vaccines and cytokines have been used as treatments and we set out to combine these two approaches by genetically engineering autologous melanoma cells to secrete interleukin 2 (IL-2). IL-2 is an important cytokine that is central to the generation of cytotoxic T cells. The rationale for using autologous tumour as a vaccine is that such material contains all the relevant antigens for a particular patient.

Preliminary work in our group demonstrated that it was possible to take melanoma cells from patients, grow them *in vitro*, and insert the IL-2 gene into these cells and they would subsequently secrete this cytokine. We treated 12 patients with metastatic melanoma and the results of this phase I/II trial were published in 1999. The main findings were that this approach was feasible and non-toxic. Patients that obtained a host response (generation of cytotoxic T cells or DTH response) had a longer progression-free survival than those who failed to generate such a response. Two patients remain alive following treatment, one of whom is disease-free at 10 years.

The problems encountered in this study were that vaccine preparation was very labour intensive and only a minority of patients who had tumour removed with the intention of preparing a vaccine, received treatment; a total of 41 patients had tumour harvested. The main reason for this was that patients progressed between harvest and the preparation of the vaccine. This finding has important implications for autologous vaccine approaches in patients with metastatic disease, as care must be taken to select patients who are not going to progress rapidly between the harvest of melanoma material and the completion of vaccine preparation.

GTAC 05: Gene therapy for metastatic melanoma: assessment of expression of DNA constructs directly injected into metastases

The aim of this project was as follows:

- To express a marker protein specifically in malignant melanoma cells *in vivo* by direct injection of DNA, as an assessment of function of a tumour-specific promoter.
- To express IL-2 specifically in malignant melanoma cells *in vivo* by direct injection of DNA, using a tumour-specific promoter.
- To assess cytokine and immunological response to melanoma after *in vivo* IL-2 expression using the above DNA construct.

Although we saw some minor evidence of expression of beta-gal, at each of the dose levels of the gene therapy, it was not consistent at any one-dose level. The IL-2 expression was difficult to assess because it was the human gene, but we did have primers to distinguish endogenous from exogenous IL-2. We also assessed the biological effects of the injection of IL-2, by analysing genes that were expressed in response to this, such as Perforin, IL-2 receptor, and TNF-alpha. Only in one patient could we see evidence of up-regulation of these genes after the IL-2 gene therapy. In terms of a response, 20 of the 23 patients had progressive disease of the lesion that was injected and at other sites. Two patients had stable disease, one was not evaluable.

Overall therefore, the conclusion was direct injection of naked DNA into lesions did not result in detectable beta-gal or IL-2 expression, in most cases, despite covering a ten-fold range in DNA concentration and those were adjusted on the basis of pre-clinical experiments for the volume of human tumours. There was no evidence of therapeutic efficacy either in the local lesion or systemically. We could not recommend the use of naked DNA in future.

GTAC 026: A study of dose requirements, safety and local efficacy of intratumoral injection of the genetically modified non-virulent herpes simplex virus HSV ICP 34.5 negative mutant 1716 into accessible soft tissue nodules of secondary malignant melanoma.

This was a proof of principle study, based on the fact that direct injection of HSV1716 into patients with CNS tumours appeared to show localisation of HSV1716 to tumour tissue and that these injections appeared to delay tumour progression (see GTAC 18, section 6.1.8).

As melanoma is derived from melanocytes, and as these cells have their origin in the neural crest, it seemed logical to establish whether or not HSV1716 either localised in human melanoma tissue, or altered the normal progression of metastatic melanoma. This was particularly worthwhile in view of the dearth of effective therapy for stage 3 and 4 melanoma. We therefore elected to inject HSV1716 into subcutaneous nodules of patients who also had metastatic melanoma elsewhere ie in lungs or liver, and who had no long term prospect of survival. We required patients with several subcutaneous nodules as one required to be biopsied to absolutely confirm the presence of melanoma in the nodule, a second was required for the HSV injection, and a third for injection of inert placebo material. We also required at least one adjacent non injected nodule to biopsy after 4 weeks to establish if there was any effect of HSV1716 on adjacent but non injected nodules. This

would suggest that the HSV1716 had stimulated an immune response which had led to a “bystander effect”.

We encountered problems with finding an adequate number of patients who had the required number of nodules, who also had systemic metastatic disease, and who wished to participate in the study, but 4 helpful patients volunteered. We observed that the HSV1716 did concentrate in melanoma tissue, but only in the injected nodule. We also observed some reduction in size of HSV1716 injected nodules, and biopsy of these showed fibrosis and necrotic tumour cells. However, we saw no evidence either of HSV1716 in adjacent non injected nodules, or of any reduction in size or fibrosis of non injected nodules.

GTAC 033: Phase I trial of immunotherapy with adenovirus-interferon gamma in malignant melanoma

In this trial, one patient was treated with local injections of the adenovirus containing gamma interferon into metastatic melanoma. The lesion injected reduced in size and there were no significant side effects. However, the patient had extensive disease and the non-injected disease inevitably progressed. Only one patient was treated with this particular virus as an improved viral vector was available for subsequent patients. This trial, similar to other ones where viruses expressing cytokine genes are injected directly into the tumour shows that they are capable of inducing an immune response, which leads to regression of the injected tumour. Unfortunately, this does not lead to any change to non-injected tumours. This one patient study formed the basis for the next generation vector, which has successfully completed a phase I study in Rochester, N.Y., U.S.A. The study was performed there for practical reasons and this study was eventually published in *Cancer Gene Therapy*, 2003, 10(4):215-9.

GTAC 38: A phase I, open label, dose escalation trial to assess the safety and immunogenicity of DISC-GMCSF in patients with metastatic melanoma

DISC-hGMCSF is a replication incompetent herpes simplex type 2 vector expressing human granulocyte macrophage colony stimulating factor. The Phase I three-centre, open label, dose escalating study DISC-hGMCSF/01 was conducted in patients with advanced metastatic melanoma, with 10 patients included in the analysis. There were two deaths due to metastatic disease progression during the study, both in the lowest dose cohort, however, neither fatality was considered to be related to the study treatment. There were three further serious adverse events which were considered to be unrelated to the administration of the trial medication. These included one case of metastatic disease progression (resulting in this patient being withdrawn from the study), one case of deep vein thrombosis and one planned hospital admission for excision of melanoma lesions. One further patient had to be withdrawn from the study due to disease progression.

DISC-hGMCSF was found to be safe and well tolerated at all dose levels (two vaccinations of 2.3×10^5 , 1.8×10^6 , or 2.5×10^7 pfu intratumourally). The injection site reaction, tenderness, was reported by most patients at some time during the study, most frequently with an NCI CTC severity grading of I. Injection site erythema and induration were reported much less frequently. All patients reported at least one systemic adverse event during the study. The most frequently reported systemic adverse events were tiredness (5

patients), ache, headache, nausea and vomiting (4 patients each). Of the adverse events classified as possibly related to treatment, few were of NCI CTC severity grades 2 or above. The majority of adverse events occurred within 7 days of treatment and of those occurring after 7 days none were of NCI CTC severity grades 2 or above.

No evidence of DISC-hGMCSF shedding was detected by infectivity assay of injection site dressings or PCR assay of serum samples. ELISA analysis of serum samples indicated that three of the nine patients who had received two vaccinations of DISC-hGMCSF had seroconverted to HSV-2 by day 28 after vaccination. No study treatment-related lymphocyte infiltration or vector-derived GMCSF RNA was detectable in the very limited number of evaluable tumour biopsy samples available.

6.1.6 Lymphoma

GTAC 010: Transfer of the human multi-drug resistance gene into the haemopoietic cells of patients undergoing high dose therapy and autologous stem cell transplantation for malignant lymphoma

The objective of this study was to transfer the MDR-1 gene into purified peripheral blood CD34+ cells obtained from patients undergoing high dose chemotherapy for malignant lymphoma. Based on prior experiments in mice, it was anticipated that successful gene transfer might confer a degree of protection against the myelotoxic effects of MDR-1 substrate drugs and that this would be accompanied by in vivo enrichment of transduced cells. The study opened for recruitment in November 1995 and closed in May 1996. A simple transduction protocol was used in which purified CD34+ peripheral blood progenitor cells were exposed for 6 hours to retroviral supernatant containing the pHaMDR-1 vector packaged in GP+env AM12 cells. The CD34 cells were washed then cryopreserved for subsequent use as autologous stem cell support for patients undergoing high dose therapy for malignant lymphoma. A total of 3 patients were entered into the study. No impairment of haematological recovery was observed using the transduced CD34 cells and there were no other adverse events. Despite the demonstration of vector derived MDR-1 cDNA in CD34 cell prior to transplant, no evidence of gene transfer was observed in bone marrow or peripheral blood cells in the post transplant period. One patient relapsed 30 months post transplant and was treated with a salvage regimen incorporating Etoposide, an MDR-1 substrate drug. No MDR-1 signal was observed in peripheral blood cells following this. There was further disease progression and the patient died 54 months post transplant. The remaining two patients remain well and in remission at 8.5 and 9 years post transplant.

The conclusion of this study was that brief exposure of haemopoietic stem cells to retroviral supernatant in the absence of growth factors has no impact on their short or long term engraftment potential although no evidence of in-vivo stem cell transduction was obtained. (Devereux *et al*, 1998, *Gene Ther* 5:403-408)

6.1.7 Head and neck cancer

GTAC 033: A dose escalating study of gene directed enzyme prodrug therapy in head and neck cancer: intratumoural injection of CTL102, a nitroreductase-encoding gene complex, with intravenous administration of the prodrug, CB 1954

Gene directed enzyme-prodrug therapy (GDEPT) seeks to accomplish tumour-targeted chemotherapy by the specific delivery, and subsequent expression of a gene, encoding an enzyme that converts a relatively innocuous prodrug, into a potent cytotoxic agent. This trial was intended to evaluate GDEPT for head and neck cancer using CTL102, a replication-defective adenovirus encoding nitroreductase (NTR). This enzyme converts the prodrug CBI954 into a bifunctional alkylating agent, capable of cross-linking DNA and initiating cell death in dividing and non-dividing cells.

The trial was designed in two stages: Stage one (Operable Arm) involved the recruitment of patients with malignancies scheduled for surgery (SSC stage 3/4 disease of the head and neck, both primary and/or metastatic) for injection of CTL102 without prodrug. A dose-escalating schedule covering 7 cohorts was devised from 1×10^8 up to 1×10^{12} viral particles with three patients per cohort. 2-5 days prior to surgery recruits received a single dose of virus by intratumoural injection. Following routine surgery histological sections from the injected tumour were examined by immunohistochemistry to identify NTR expression within the malignant and surrounding normal tissue. This stage of the trial aimed to identify the minimum, safe dose of the virus that gave an extent of NTR expression likely to yield anti-tumour effects in combination with CBI954. Once this minimum dose was determined the second stage of the study was to be initiated. Stage two (Inoperable – therapeutic arm) was aimed at patients with recurrent or persistent disease following surgery, radiation, or chemotherapy and for whom no further conventional therapy was indicated. Three patients were to be recruited to each cohort receiving a single intratumoral injection of CTL102 followed 2 days later by an IV infusion of CBI954 prodrug. The dose of CTL102 was initiated at the minimum dose determined in the operable arm and was to be escalated in log stages to a maximum of 1×10^{12} viral particles. This stage of the trial aimed to assess the safety and anti-tumour effects of the virus/prodrug combination.

This multi-centre study was initiated at UK and other European centres in 2001 and had only recruited seven patients to the operable arm by 2003. Limited expression of the transgene was seen at viral doses of 1×10^{10} and 1×10^{11} with no significant toxicity. Due to poor recruitment the trial was closed in April 2003.

GTAC 050: HSV1716 in squamous cell carcinoma of the head and neck

All 20 patients recruited into this study tolerated the intratumoural injection of HSV1716 very well, and none experienced any toxicity. Oral squamous cell carcinomas are generally very accessible, and easily injectable under local anaesthetic. HSV1716 DNA positive blood samples post injection indicated entry into the systemic circulation and a subclinical viraemia. An immune response was identified in two patients having seroconverted within 3 weeks of their injection. Until the efficacy of HSV1716 in HNSCC has been determined, the importance of HSV immune status remains unclear. Identifying HSV1716 DNA by PCR in tumour distal to the site of injection indicated replication in one patient. This was not supported by positivity in immunohistochemistry. Three tissue samples positive for HSV1716

DNA by PCR at 72 hours indicated viral survival for this length of time, but there were no signs of necrosis specifically attributable to HSV1716 in the tumour. The dose of HSV1716 injected and the mode of delivery may explain the minimal evidence of viral replication. Squamous cell carcinoma cells are tightly packed and may not have been exposed to virus. A higher dose of HSV1716 and multiple injections need to be considered for future clinical trials.

This study demonstrated conclusively that HSV1716 can be injected into patients with oral squamous cell carcinoma easily and with no concomitant toxicity. Further clinical studies are now indicated to establish the efficacy of HSV1716 in head and neck squamous cell carcinoma.

6.1.8 Brain cancer

GTAC 018: Gene therapy for glioblastoma

Three Phase I clinical trials have been carried out in patients with malignant brain tumours using HSV1716, a modified version of Herpes Simplex Virus (or the virus that causes cold sores). The virus has been modified so that it is unable to replicate in normal cells, but in actively dividing cells, such as cancer cells, it can multiply and kill the cell.

Study 1 was designed to demonstrate the ‘proof of principle’ that HSV1716 could be injected directly intratumourally in patients with recurrent glioblastoma in doses that, from animal studies, are likely to produce an antitumour effect. Nine patients were recruited. All demonstrated active malignant glioma at biopsy immediately before injection. The majority were heavily immunocompromised. All but one had antibodies against herpes virus (i.e. were seropositive for HSV). There were 7 glioblastomas, one anaplastic astrocytoma and one oligodendroglioma. HSV1716 was injected directly into the recurrent tumours using a multi-point injection technique (up to 10 injections per patient). Doses of 10^3 to 10^5 plaque forming units were used. Patients were intensively followed for 6 days as inpatients with daily clinical analysis, haematological, biochemical, immunological and radiological investigations. They were followed thereafter as outpatients until the present time or to death.

An extension to the first study has also been completed in which an additional ten patients were treated according to the same protocol regimen. Three patients in this supplementary group received a dose of 10^5 pfu while seven patients received a dose of 10^6 pfu on a single occasion. No patient experienced toxicity associated with the administration of HSV1716.

Study 2 was designed to demonstrate the proof of principle that HSV1716 was capable of infective replication when injected intratumourally into patients with glioblastoma but remained a safe procedure. Twelve patients were injected with HSV1716. All proceeded to tumour resection and 11 have received further anticancer treatment post operatively. There were 11 glioblastomas and one anaplastic astrocytoma. Six patients were measurably immunocompromised. 10 were seropositive, two seronegative for HSV. Patients were injected intratumourally with 10^5 pfu of HSV1716 and followed post operatively as in study 1. Between 5 and 9 days later the tumours were excised and submitted for viral analysis. Post operatively patients were treated with either chemotherapy or radiation therapy. Safety and radiological data were collected lifelong or to the present. No patient experienced toxicity.

In a third clinical study in glioma, HSV1716 was injected into the brain surrounding tumour immediately following tumour resection in four patients with recurrent GBM and six with *de novo* GBM as well as one with an anaplastic astrocytoma and one with an anaplastic oligodendroglioma. All but one went on to receive further standard treatment. One patient in this trial showed remarkable clinical improvement and there was imaging evidence of reduction in residual tumour over a 22 month period despite no further medical intervention at that time. His clinical response was of particular note given his very poor pre-operative condition and the size of his tumour. In addition he declined all other adjuvant treatments.

Three of the patients in this trial were seronegative for HSV-I antibody. Two seroconverted 3 to 4 weeks after virus injection. The third did not seroconvert. Serum samples from four patients were positive for HSV DNA; of these three were seropositive and had prior clinical history of HSV infection (cold sores). The fourth was seronegative and seroconverted at the time that HSV DNA was detected in the blood sample. None of the twelve patients demonstrated evidence of clinical toxicity associated with HSV1716.

One patient from the first trial received a second injection of HSV1716 at a dose of 10^5 pfu approximately 34 months after the first injection. One patient from the third trial received a second and a third injection of HSV1716 at a dose of 10^5 pfu approximately 26 and 28 months after the first injection respectively. These were administered following imaging evidence of tumour recurrence. No toxicity attributable to HSV1716 was identified in either patient.

None of the 43 patients at any time showed any clinical or radiological evidence of toxicity due to injection of HSV1716. The toxicity of post-operative treatment in patients following injection with HSV1716 was no greater than expected in uninjected patients. Evidence of HSV1716 replication in tumour tissue has been obtained in the majority of the patients in the second study. Two patients from the original 9 in study 1, two from the extension to study 1 and three patients in study 3 remain alive at times up to 80 months following treatment with HSV1716.

From these studies it has been concluded that HSV1716 can be given safely as an intratumoural injection or into brain surrounding tumour to patients with newly diagnosed or recurrent malignant glioma. This safety is demonstrated in patients who seroconvert, who show evidence of intratumoural HSV1716 proliferation and in patients undergoing immunosuppressive therapy with steroids, chemotherapy and radiotherapy. No patient has suffered HSV treatment related toxicity. The demonstration of HSV1716 proliferation in tumour tissue gives hope that HSV1716 may be a useful therapy for patients with brain tumours.

6.1.9 Multiple cancers

GTAC 060: Study of transfection efficacy and safety of MetXia-OB83 in patients with cutaneous lesions of breast cancer or melanoma

PRIMARY OBJECTIVES

1. To assess the safety of ascending doses of MetXia injected into cutaneous tumour nodules of adenocarcinoma of the breast or melanoma.
2. To assess gene transfer efficiency in these tumours.
3. To assess the gene expression efficiency of *lacZ* marker and cytochrome P450 2B6 genes in these tumour nodules.
4. To assess biodistribution of the vector, genes and gene products in tumour and in the blood.
5. To assess the immunological response to vector components and transgenes.

SECONDARY OBJECTIVES

1. To assess the macroscopic tumour response to treatment with MetXia in combination with oral administration of cyclophosphamide.
2. To assess the histological and biochemical response of tumours to treatment with MetXia in combination with oral administration of cyclophosphamide.

SUMMARY

The treatment regime of MetXia-OB83 and cyclophosphamide was well tolerated by all 9 patients in the study. A total of 50 adverse events were experienced by patients participating in the trial. In 11 cases the events were considered to be definitely, possibly or probably related to study therapy by the investigator. The event was considered to be unrelated to study therapy in 39 cases. Cyclophosphamide was considered to be a causative agent in 17 events. The majority of adverse events were associated with the body system category of general disorders and administration site conditions. Six patients completed the nine week monitoring period. Seven patients showed either *de novo* or significantly enhanced (≥ 2 fold) immunological responses to 5T4 or CEA following administration of MetXia. Biopsies from all BC2 patients showed 3 to be positive for 5T4 expression and 7 to be positive for CEA. Anti vector antibody responses were detected in patients enrolled in the 100x group who remained on trial for greater than three weeks. Western blot analysis showed this antibody response to be specific for Gag. No patient in the 10x group showed a vector specific antibody response. Gene transfer was detected by quantitative PCR for MetXia-OB83 specific DNA sequence in biopsies from all patients at the 10x and 100x doses. Gene transfer was also detected by histological staining for the *lacZ* marker. This was found in all patients at a level of $< 1\%$, except patient 204 which showed gene transfer of 1-10%. However, no clear correlation between the levels of gene transfer and dose administered could be determined. The BC2 study closed early due to difficulties in recruiting and a lack of apparent response to MetXia.

6.2 HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

GTAC 037: Evaluation of two therapeutic HIV vaccination regimens in HAART-treated primary HIV infection (PHI) subjects following analytical treatment interruption: results of a randomised, double-blind, placebo-controlled study (QUEST; PROB3005)

BACKGROUND. Preliminary results from this trial showed that initiation of HAART at the time of PHI resulted in significant and sustained suppression of plasma HIV-1 viral load (pVL) over 48 weeks. This randomised, double-blind, placebo-controlled trial was conducted to assess the impact of therapeutic HIV vaccination on pVL following analytical treatment interruption.

METHOD. Seventy-nine adult subjects from 25 centres (Europe, Australia and Canada) on long-term (1.5 to 5 years) suppressive HAART were randomised to receive over 24 weeks either placebo, Alvac HIV vCPI452, or Alvac HIV vCPI452 + Remune, followed by discontinuation of HAART. The primary efficacy end-point was the difference of placebo versus pooled vaccine arms in proportions of subjects at 24 weeks following HAART discontinuation.

RESULTS. Pre-vaccination demographic characteristics were similar between treatment arms. All subjects completed the vaccination schedule and initiated the analytical treatment interruption, seven of whom restarted HAART before week 24. Overall there was no statistically significant difference between the placebo and vaccine groups. No subjects had disease progression. Adverse events were similar across the groups with no reported serious treatment related adverse events and no subjects discontinued the vaccination phase because of adverse events.

CONCLUSIONS. This first randomised, double-blind study of therapeutic HIV vaccination in HAART treated subjects failed to demonstrate a significant benefit of vaccination over placebo in terms of pVL control after HAART discontinuation. Further immunological analyses will determine if the vaccine regimens resulted in significant HIV-1 specific cellular immune responses. High compliance (100%) and low rate of adverse events suggest these vaccine regimens were well tolerated.

GTAC 053: A pilot study of the safety and immunogenicity of a candidate HIV-1 clade A DNA vaccine, pTHr.HIVA, given by needle injection into the deltoid muscle in HIV-1-seropositive subjects receiving highly active antiretroviral therapy (HAART)

STUDY AIM. To evaluate the safety and immunogenicity of pTHr.HIVA as a therapeutic vaccine for HIV-1 infection, prior to inclusion in prime-boost immunisation schedules.

INCLUSION CRITERIA AND IMMUNISATION SCHEDULE. Ten HIV-1-seropositive individuals who had been treated with HAART for at least one year and who had a CD4 T cell count of > 300 cells /ml and undetectable viral load (Viral load < 400 copies / ml, as an ultra-sensitive assay was not available at the time the study was conducted) were selected to receive two 500µg doses of DNA by intramuscular injection three weeks apart. There were no unvaccinated controls. Although the vaccine was based on the HIV-1 clade A consensus sequence, subjects infected with non-A subtypes were included.

RECRUITMENT, IMMUNISATION AND FOLLOW-UP. Ten subjects were recruited between August 2002 and February 2003. All ten subjects completed the immunisation schedule according to the protocol, except one volunteer in whom the second immunisation was delayed by three days as the receipt of a blood result (anti-DNA antibodies) was delayed. All subjects completed scheduled follow-up to day 105. After the protocol was amended to extend follow-up to one year, eight subjects attended for a 6 month and a 12 month visit. Confirmation that the two subjects who did not attend were alive and well was obtained from their hospital records.

Safety and tolerability. There were no serious or severe adverse events. There were 30 non-serious adverse events, all of which were grade 1 or 2 and all were categorised as ‘possibly’, ‘unlikely’ or ‘unrelated’ to vaccination. Local and systemic reactions to the vaccine were non-existent or trivial. There was no significant change in CD4 lymphocyte count in any subject after immunisation. Plasma viral loads remained undetectable in all subjects throughout the study except in one subject on one occasion. This individual reported missing a single dose of his antiretroviral medication two weeks before the first immunisation. No subject has developed anti-DNA antibodies following immunisation.

Immunogenicity. CD8+ and CD4+ T cells specific to the vaccine immunogen (HIV-1 clade A gag and CTL epitopes) were quantified using two laboratory assays employing the detection of interferon- γ (Elispot assay and intracellular cytokine assay). 8/10 subjects had detectable responses prior to immunisation, indicating recognition of viral sequences shared between the patients’ own virus and the vaccine sequence. Overall, there was no significant boosting of CD8+ or CD4+ T cell responses after DNA immunisation although an increased frequency of vaccine-specific CD8+ T cells and new CD4+ T cell responses were observed in three volunteers.

CURRENT AND FUTURE WORK. A study investigating the safety and immunogenicity of a related product, MVA.HIVA, which comprises modified vaccinia virus Ankara recombinant for the same HIV-1 insert, is ongoing (GTAC 079). We are seeking approval to immunise the volunteers in GTAC 053 with MVA.HIVA.

LESSONS LEARNT. Very few studies of this nature have been conducted in humans worldwide, therefore, this study has provided further evidence that recombinant DNA vaccines are safe and well tolerated in human subjects with chronic HIV-1 infection. The lack of immunogenicity is not entirely surprising, given that immunogenicity of DNA alone has been poor in animal studies. However, it will be important to ascertain whether pTHr.HIVA has primed new responses which could be boosted by MVA.HIVA. The participants were a motivated group who express continued interest in therapeutic vaccine studies. This work was presented at the 10th Conference on Retroviruses and Opportunistic Infections in Boston, USA 2003. A manuscript has been submitted to *AIDS*.

GTAC 075: A phase I study of NYVAC C in healthy volunteers at low risk of HIV infection (EV01)

24 healthy male and female volunteers in London and Lausanne who are at low risk of HIV infection were entered into the study and randomly allocated to receive two intramuscular injections of one of the following two products at weeks 0 and 4. Twenty volunteers

received NYVAC HIV-C and four placebo. Participants, clinical investigators and cellular immunologists were blind to the allocation.

Participants attended one of two clinical centres (Centre Hospitalier Universitaire Vaudois, Lausanne, and St Mary's Hospital, London) on at least 8 occasions over 12 weeks, and then at 6 and 12 months. Participants had blood and urine collected, and received two immunisations. They were counselled prior to and following a HIV test, and given health education on prevention of sexually transmitted infections including HIV. The primary objective is to explore the safety and immunogenicity of NYVAC C, and the respective end-points are grade 3 or above local (pain, rash, swelling), general (fever, chills, headache, nausea, vomiting, malaise, myalgia) or other unsolicited adverse events, and cellular responses assessed using the ELISPOT technique.

METHODS. Safety data were collected systematically by staff on events that are recognized to be associated with licensed vaccines (solicited events) prior to immunization, one hour, within three days and one week following immunization. One Swiss participant missed the three day visit after the second immunization due to difficulties in getting to the clinic, but otherwise these data are complete. In addition, volunteers were asked to complete diary cards describing the same solicited events on a daily basis for seven days following immunization, or longer if events were ongoing. All participants completed diary cards. At every visit from enrolment on, volunteers were asked whether there were any new events or changes to existing events, and new or changes to medication. Events were graded according to the protocol and assessed for relationship to study product (unrelated, unlikely, possibly or probably).

RESULTS up to and including week 24. There have been no serious or severe (grade 3) events to date, other than the admission of two volunteers for elective surgery for pre-existing conditions, one for lipo-suction and one to repair an inguinal hernia. There were no moderate local reactions following the first immunization and only one after the second (swelling of greater than 25% but less than 50% of the baseline arm circumference recorded by a participant on a diary card). The most common solicited local reaction was pain at the injection site. Four volunteers reported moderate systemic events (chills/rigors, malaise, myalgia, headache, nausea), three following the first immunization and one following the second. The most common solicited systemic reaction was malaise. The median duration of solicited events was 2 days and the inter-quartile range was slightly longer (1-3 days) following the second immunization compared to the first (1-2 days).

All of the volunteers reported at least one non-solicited adverse event during follow-up. Sixty eight events in 24 volunteers were considered mild (grade 1) and 14 events in 12 volunteers moderate (grade 2). Eight events were considered possibly or probably related to study product, only one of which was moderate and this was fatigue occurring in a CHUV participant 10 weeks after the first immunization. This event was associated with mild weight loss (3kg from a baseline of 65kg), and both were considered possibly related. Complete resolution occurred after 12 weeks.

SUMMARY. This trial remains blind to allocation, but to date the vaccine products have been well-tolerated and the reactions following immunisation consistent with those seen following immunization with licensed vaccines. There have been no Serious Adverse Events considered to be Reactions reported during the trial.

6.3 SINGLE GENE DISORDERS

GTAC 02, 07, 08, 015: Gene therapy for cystic fibrosis (nasal trials)

Note: This information was published in the Seventh Annual report but is included here for completeness.

Cystic fibrosis (CF) is one of the most common, serious genetic diseases in the UK. Gene therapy is considered as a possible treatment for CF lung disease, which is the major cause of mortality in CF individuals. In these studies, a non-viral gene transfer vector, in which plasmid DNA is complexed with cationic liposomes, has been employed.

Two double-blinded clinical studies, each involving 12 CF patients, in which a gene transfer formulation was administered to the nasal epithelium have been completed by the research group. The studies aimed to test the safety and efficacy of single and multiple doses. The results showed no evidence of inflammation, toxicity or an immune response towards the DNA/liposomes or the CF protein. Nasal epithelial cells were collected after each of three doses for a series of efficacy assays to measure vector DNA and mRNA, CFTR protein, bacterial adherence, and halide efflux *ex vivo*. Airway ion transport was also assessed *in vivo* throughout the studies. In the first single-dose study, gene transfer was detected in six of the eight treated patients, although the gene transfer was modest and transient, indicating that repeated administration is likely to be required for long-term gene expression. The results showed that DNA/liposomes could be successfully re-administered to the nasal epithelium without apparent loss of efficacy.

In conclusion, these studies and others have demonstrated proof of principle for CF gene therapy. Current research is now focused on improving the efficiency and duration of CF gene transfer in the lung.

GTAC 013: A proposal to study the efficacy of transplantation of autologous retrovirally transduced bone marrow in patients homozygous for the W402X mutation (Hurlers syndrome)

This trial used a moloney-murine leukaemia-based retroviral vector (LX) expressing the cDNA encoding human alpha-L-iduronidase (IDUA). Overall, three patients were treated during this trial. Initially, two were treated with subablative conditioning at (cyclophosphamide 50mg/kg), prior to infusion of gene-modified cells. On follow-up, it was evident that both patients had experienced minimal bone marrow suppression and had non-detectable leukocyte IDUA activities following reinfusion of the transduced bone marrow. Consequently these two patients underwent a further bone marrow harvest, at bone marrow recovery and were subsequently retreated with myeloablative chemotherapy (Busulphan 4mg/kg/day on 4 consecutive days followed by cyclophosphamide 60mg/kg/day over the following 2 days), before a second infusion of genetically manipulated bone marrow. A third patient underwent conditioning with busulphan and cyclophosphamide as their first and only procedure.

At completion of the transduction procedure, IDUA activity was determined in the cultured bone marrow cells and had risen from 0.0 $\mu\text{mol/g protein/hr}$ to between 8.8 and 42 $\mu\text{mol/g protein/hr}$ (median activity 28 $\mu\text{mol/g protein/hr}$, normal range 5-30 $\mu\text{mol/g protein/hr}$).

Despite significant cell loss during transduction patients were administered genetically modified bone marrow containing $0.67\text{-}1.2 \times 10^8$ nucleated cells/kg (median $1.0 \times 10^8/\text{kg}$). All patients tolerated the initial infusion with minimal problems, a single patient experiencing a transient febrile reaction. Bone marrow recovery as defined by time to 0.5×10^9 neutrophils/l, occurred by day 15 in patients conditioned with cyclophosphamide alone and by day 27 following more intensive pre-conditioning. Patients receiving the sub-ablative conditioning had 1 and 0 days of thrombocytopenia respectively, whereas the duration was 6-17 days following the more intensive pre-conditioning.

No IDUA activity could be detected in the circulating white cells at the point of bone marrow recovery in either of the two patients conditioned with cyclophosphamide alone. When patients received a more intense myeloablative conditioning prior to transplant, a transient increase in IDUA activity was detected in white blood cells. IDUA activity rose to a peak level, equivalent to $\sim 10\%$ of normal human controls at day 18/19 in all three patients and then gradually declined to non-detectable levels over the following 12-40 days. The peak of IDUA activity in each patient was accompanied by a rise in circulating antibody to IDUA protein. As the IDUA activity declined there was a concomitant decrease in antibody titre to IDUA protein. Bone marrow was obtained from patients at 2 months post-transplantation and assessed by semi-quantitative PCR for the presence of IDUA cDNA. These analyses indicated that the level of transgene positive cells in the bone marrow of the individuals at this time was low (around 0.01%), consistent with the loss of L-iduronidase activity and apparently graft rejection.

CONCLUSIONS. An immune response to transgene product, likely in concert with poor transduction of long-term repopulating cells, led to only transient and minimal correction of IDUA deficiency in these patients.

SECTION 7: UPDATE ON GENE THERAPY WHITE PAPER COMMITMENTS

The Government's 2003 "Genetics" White Paper: Our Inheritance, Our Future – realising the potential of genetics in the NHS" made the following commitments about funding gene therapy research:

- 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. (Paragraph 5.24)
- The Department of Health will make available £2.5 million over 5 years to support gene therapy research for cystic fibrosis. (Paragraph 5.25)
- 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. (Paragraph 5.27)
- 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. (Paragraph 5.28)

The allocation of the £3 million for single gene disorders, and the £1 million for long-term safety work, were announced by Health Secretary John Reid in March 2004. The following teams were supported:

- £1,600,000 to the Muscular Dystrophy Campaign for research on Duchenne muscular dystrophy (DMD). DMD is a rare disorder with onset in early childhood. Progressive disability due to muscle breakdown is typically followed by death in the early twenties. There are no effective treatments. This will be the first UK gene therapy trial aimed at treating DMD.
- £900,000 to the Institute of Child Health, University College London, for gene therapy research on one form of inherited retinal disease, childhood blindness. There are no effective treatments. This will be the first UK gene therapy trial aimed at treating eye disorders.
- £500,000 to Oxford BioMedica for research on Haemophilia A. Haemophilia is a blood condition in which an essential blood-clotting factor is either partly or completely missing. If left untreated internal bleeding into joints, muscles and soft tissues can cause acute pain and severe joint damage. Haemophilia A is due to a mutation in the gene that produces blood-clotting Factor VIII. This will be the first UK gene therapy trial aimed at treating Haemophilia.
- £450,000 to the University of Glasgow for research on the safety of retroviral vectors. This work addresses some of the recommendations for research looking at the safety of gene therapy made by the joint April 2003 working group of GTAC and the Committee on Safety of Medicines.

- £200,000 to the Royal Free and University College London Medical School for research on the safety and efficacy of adeno-associated vectors for the purpose of genetic diseases affecting the liver, such as Haemophilia B. Haemophilia B is due to a mutation in the gene that produces blood-clotting Factor IX.
- £200,000 to the Rayne Institute, Kings College London, for research on liver disease gene therapy, using hydrodynamic gene delivery. This is a new and promising technique for the administration of gene therapy products. It involves delivering the gene therapy drug under conditions of rapid infusion of large fluid volumes.
- £125,000 to University College London for research on engineering retroviral vectors. This work addresses some of the recommendations for work looking at the safety of gene therapy made by the joint April 2003 working group of GTAC and the Committee on Safety of Medicines.

The successful applicants for the support for gene therapy of cystic fibrosis were announced by Health Minister Lord Warner in January 2005. Money was awarded to the UK Cystic Fibrosis Trust and Gene Therapy Consortium for “Vector testing, selection of clinical trial material and clinical trials on gene therapy for cystic fibrosis” and to the Institute of Child Health for “Gene therapy for cystic fibrosis in children nebulised delivery of a synthetic vector formulation to the nose, comparisons of vector formulations”.

The remaining commitment to spend £4 million on providing access to clinical grade gene therapy vectors is yet to be implemented.

SECTION 8: ANNEXES

ANNEX A: GLOSSARY

AV

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.

Antisense

Each protein in the body is coded for by a stretch of DNA/RNA. Antisense DNA/RNA binds to this stretch of DNA/RNA to block or modify the production of the protein.

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.

DNA (deoxyribonucleic acid)

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

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 contains several billion 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 or 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.

Vaccine

A product (for example, gene therapy vector) designed to boost immunity to a disease by stimulating the immune system.

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.

Further glossary: <http://www.genome.gov/glossary.cfm>

ANNEX B: TERMS OF REFERENCE

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

- (1) To consider and advise on the acceptability of proposals for gene therapy research on human subjects, on ethical grounds, taking account of the scientific merits of the proposals and the potential benefits and risks;
- (2) To work with other agencies which have responsibilities in this field including local research ethics committees and agencies which have statutory responsibilities – the Medicines and Healthcare products Regulatory Agency (MHRA), the Health and Safety Executive, and the Department for Environment Food and Rural Affairs (DEFRA);
- (3) To provide advice to UK Health Ministers on developments in gene therapy research and their implications.

The Committee has a responsibility for:

- (a) Providing advice for applicants on:
 - (i) The content of proposals, including the details of protocols, for gene therapy research on human subjects;
 - (ii) The design and conduct of the research;
 - (iii) The facilities necessary for the proper conduct of the research;
 - (iv) The arrangements necessary for long term surveillance and follow up.
- (b) Receiving proposals from doctors who wish to conduct gene therapy research on human subjects, and making an assessment of:
 - (i) The clinical status of the subjects;
 - (ii) The scientific quality of the proposal;
 - (iii) The scientific requirements and technical competence necessary for carrying out gene therapy research effectively and safely;
 - (iv) Whether the clinical course of the particular disorder is known sufficiently well for the outcomes of therapy to be assessable;
 - (v) Sound information, counselling and advice to be given to the subject (or those acting on behalf of the subject);
 - (vi) The potential benefits and risks for the subject of what is proposed.

ANNEX C: MEMBERSHIP OF GTAC

GTAC Members

- Professor Norman Nevin (Chairman),
Emeritus Professor of Medical Genetics, Queen's University, Belfast.
- Dr Richard Ashcroft
Medical Ethicist, Imperial College London
- Mrs Deborah Beirne,
Senior Research Nurse, St. James Hospital, Leeds
- Dr Caroline Benjamin,
Macmillan Genetic Counsellor, Liverpool Women's Hospital NHS Trust
- Professor Martin Gore, vice Chairman (since May 2004)
Consultant Medical Oncologist, The Royal Marsden Hospital, London
- Professor Terence Hamblin,
Consultant Haematologist, University of Southampton and Royal Bournemouth
Hospital
- Dr Peter Harris,
Development Director, KuDOS Pharmaceuticals Ltd.
- Professor David Harrison,
Professor of Pathology and Medical Researcher, Department of Pathology, Edinburgh
University
- Mr Michael Harrison, alternate vice Chairman (since May 2004)
Barrister, London
- Professor Nicholas Lemoine,
Professor of Molecular Pathology, Cancer Research UK Molecular Oncology Unit,
Hammersmith Hospital, London
- Dr Adrian Lepper
Chartered engineer, Hertfordshire
- Professor Andrew Lever,
Professor of Infectious Diseases, University of Cambridge
- Professor Alex Markham,
Professor of Molecular Medicine, University of Leeds
- Professor James Neil
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

Medicines and Healthcare products Regulatory Agency (MHRA):

- Dr Philip Harrison

Health and Safety Executive:

- Dr Michael Mackett

Secretariat (Department of Health)

- Dr Monika Preuss
- Dr Cathleen Schulte (from September 2004)
- Dr Jayne Spink
- Ing. Daniel Gooch
- Mrs Margaret Straughan

ANNEX D: REGISTER OF MEMBERS INTERESTS

GTAC Member	Declared interests
Professor Norman Nevin	None
Professor Nick Lemoine	Consultant for IC-Vec and Medical Solutions Ltd
Dr Caroline Benjamin	Husband employed as Finance Manager for ConvaTec, Bristol Myers Squib, UK
Professor Martin Gore	<ul style="list-style-type: none"> • Ad hoc consultancy to Schering-Plough, Bristol Myers Squib, Aventis, Novartis, Pierre Fabre, Debiopharm, Chiron, 3M, Centocor, Merck, Pfizer, GlaxoSmith Kline, Novo Nordisk, Bayer and KuDOS • Consultant, Cambridge Antibody Technology
Professor Terence Hamblin	Ad hoc consultant to and research funds from Schering AG, Roche and Celgene.
Mr Michael Harrison	<ul style="list-style-type: none"> • Managing director of Bioethics Consulting Ltd. • Independent practising barrister working in the field, interests are declared as appropriate
Professor David Harrison	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none">• 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 E: EXTERNAL EXPERT ADVISERS TO GTAC

GTAC is extremely grateful to all its expert advisers for their support in the review of applications and for their input of expertise and advice in 2004. These included:

- Professor Jane Apperley, Hammersmith Hospital, Imperial College London
- Dr Andrew Baker, Division of Cardiovascular and Medical Sciences, University of Glasgow
- Professor Mary Collins, Division of Infection and Immunity Royal Free and University College Medical School, London
- Dr Huw Davies, Irvine Center for Virus Research, University of California, USA.
- Dr Sarah George, Bristol Heart Institute, University of Bristol
- Professor Robert Hawkins, Medical Oncology, Christie Hospital, Manchester
- Dr Simon Hollingsworth, Royal Free & University College Medical School
- Dr Sarah Howie, Department of Pathology, University of Edinburgh
- Dr Keith Leppard, Department of Biological Sciences, University of Warwick
- Professor Pedro Lowenstein, Cedars-Sinai Medical Center, Los Angeles, USA
- Professor Norman Maitland, Department of Biology, University of York
- Professor Michael Marber, Cardiovascular Research Division, King's College London
- Professor Paul Moss, Institute for Cancer Studies, University of Birmingham
- Dr Christopher Newman, Cardiovascular Research Unit, Sheffield University
- Dr Christian Ottensmeier, Cancer Sciences Division, Southampton University Hospitals
- Professor Poulam Patel, Academic Division of Clinical Oncology, University of Nottingham
- Dr Silvia Quarantino, Cancer Sciences Division, Southampton University Hospitals
- Dr Linda Scobie, Institute of Comparative Medicine, University of Glasgow
- Dr Peter Searle, Institute for Cancer Studies, University of Birmingham
- Dr Sunil Shaunak, Department of Infectious Diseases, Hammersmith Hospital, London
- Professor Peter Stern, Paterson Institute for Cancer Research, Christie Hospital, Manchester
- Professor Jonathan Stoye, Division of Virology, National Institute for Medical Research
- Professor Jonathan Waxman, Clinical Oncology Section, Hammersmith Hospital

ANNEX F: SUMMARY OF UK GENE THERAPY TRIALS 1993–2004

AN ANALYSIS OF UK CLINICAL GENE THERAPY: 1993 – 2004

Since 1993, when the first gene therapy study was conducted in the UK, GTAC has processed 110 applications to do clinical trials. Of these, 100 applications were approved (or conditionally approved) and four approved trials were subsequently withdrawn. The remaining 96 gene therapy trials, open and closed, are analysed below.

In these 96 trials, 894 patients were enrolled by December 2004 (711 patients by December 2003). The following three figures analyse the studies in terms of the year in which they were approved (Figure 1), the vector system used to deliver the therapeutic genes (Figure 2), and the disease (Figure 3). As shown in Figure 3, almost three quarters of all approved UK gene therapy trials, 68 in total, are for the treatment of cancers. Figure 4 breaks down this data in more detail.

Tables 1 and 2 show where UK gene therapy stands in relation to trials in Europe and worldwide, respectively (source: The Journal of Gene Medicine, Dec 2004).

Figure 1: GTAC approved trials (open and closed) by year (n = 96).

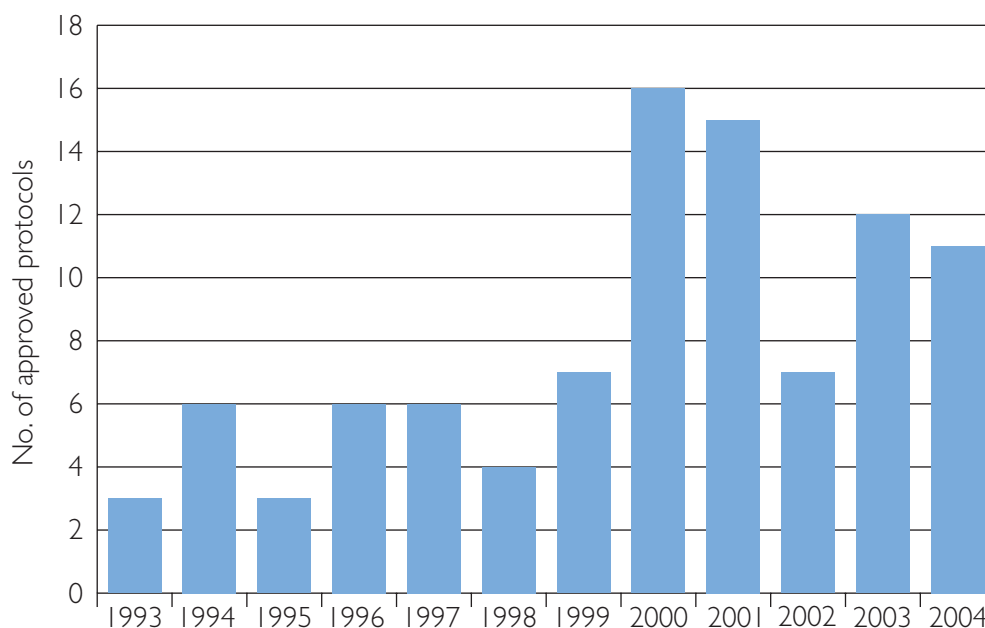


Figure 2: GTAC approved trials by vector system (n = 96).

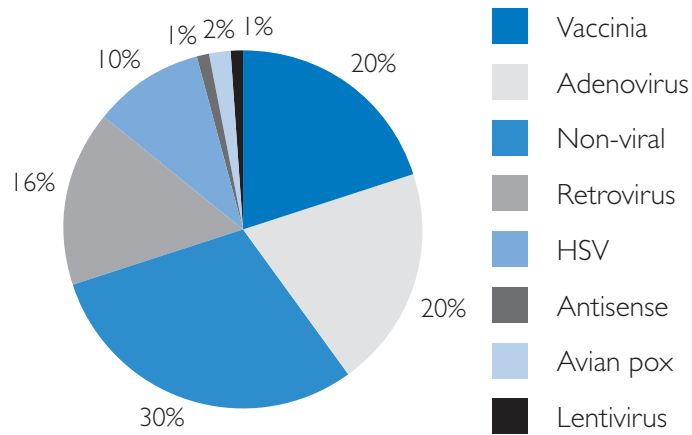


Figure 3: GTAC approved trials by disease (n = 96).

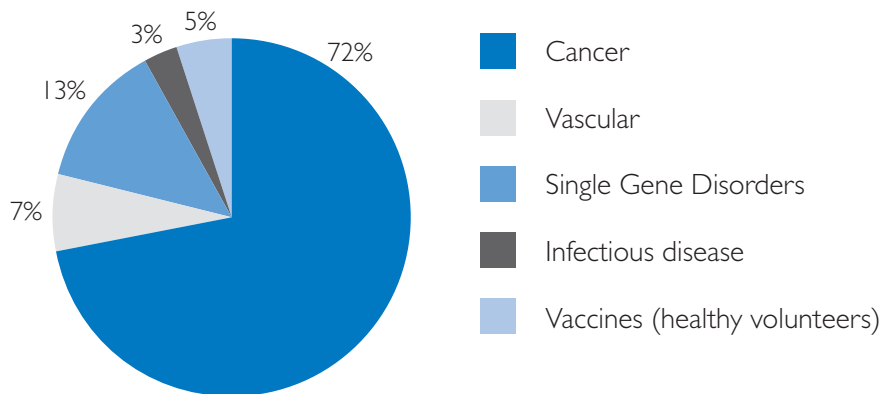


Figure 4: GTAC approved cancer trials (n = 68).

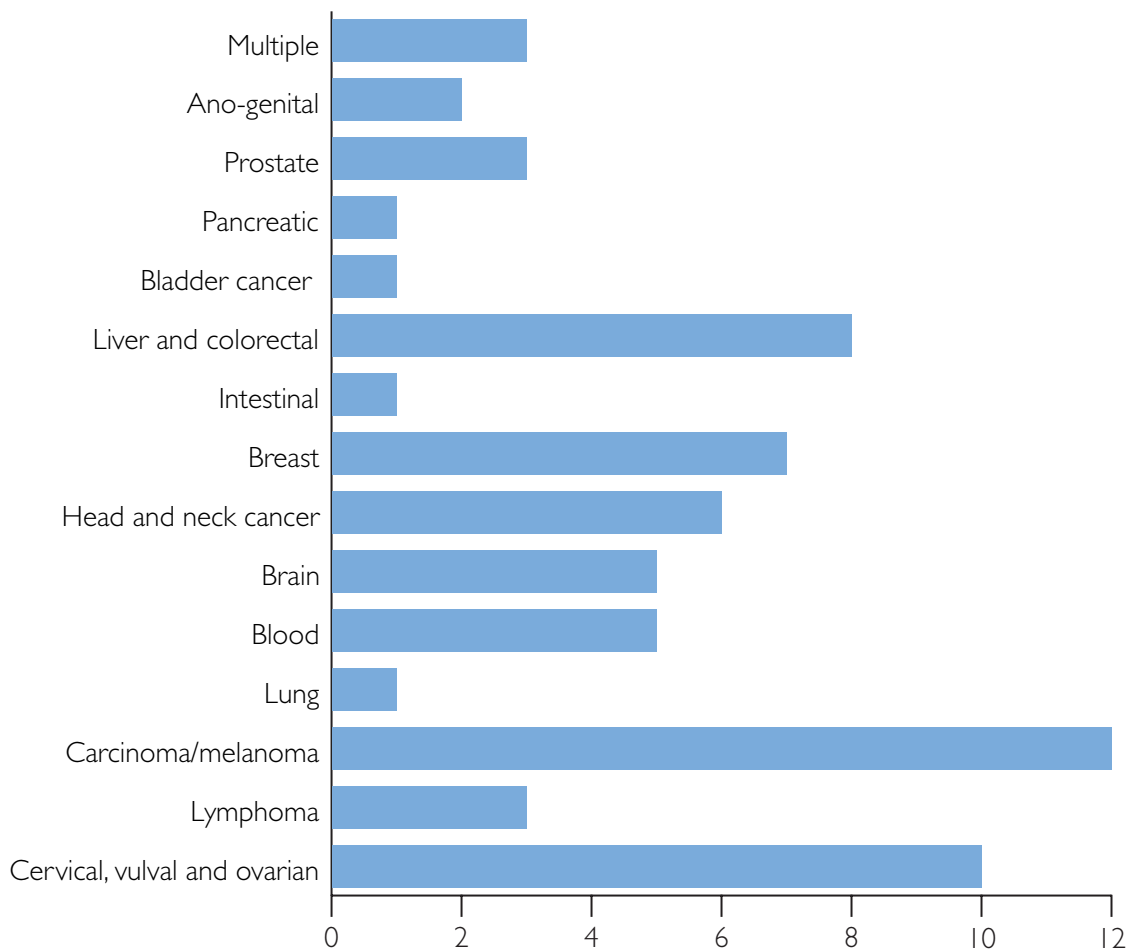


Table I: Gene Therapy trials in Europe (source: Journal of Gene Medicine)

Austria	0.7%
Belgium	6.1%
Czech Republic	0.4%
Finland	1.1%
France	6.5%
Germany	22.7%
Italy	3.6%
Netherlands	2.2%
Norway	1.4%
Poland	1.1%
Spain	1.1%
Sweden	0.7%
Switzerland	12.3%
UK	40.1%

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

Australia	1.5%
Austria	0.2%
Belgium	1.7%
Canada	1.2%
China	0.3%
Czech Republic	0.1%
Egypt	0.1%
Finland	0.3%
France	1.8%
Germany	6.5%
Israel	0.2%
Italy	1.0%
Japan	1.0%
Mexico	0.1%
Netherlands	0.6%
New Zealand	0.2%
Norway	0.4%
Poland	0.3%
Singapore	0.2%
South Korea	0.2%
Spain	0.3%
Sweden	0.2%
Switzerland	3.5%
UK	11.4%
USA	66.5%

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 “Suspected Unexpected Serious Adverse Reaction” (SUSAR) as well as of any “Serious Adverse Event” (SAE).

© Crown copyright 2005

267413 1p 1k Mar 05 (CWP)

The GTAC Secretariat may be contacted at:

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

267413/*Gene Therapy Advisory Committee: Eleventh Annual Report* can also be made available on request in braille, on audio-cassette tape, on disk and in large print.

This report is also on our website:
www.advisorybodies.doh.gov.uk/genetics/gtac