Annual report : 2002 / Gene Therapy Advisory Committee.

GENE THERAPY ADVISORY COMMITTEE

NINTH ANNUAL REPORT

Covering the period from January 2002 to December 2002

Health Departments of the United Kingdom
2003

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The GTAC Secretariat may be contacted at:

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

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

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FOREWORD

Fifty years ago, Watson and Crick built a three-dimensional model of DNA (deoxyribonucleic acid) that showed by its structure, how DNA was the key molecule of heredity. They had made a discovery that has transformed science and medicine, although the full impact has yet to be felt.

In 1990, the Human Genome Project (HGP), an international enterprise to sequence human DNA was launched. The HGP ends in 2003 with the completion of the human genetic sequence. A working draft of the entire human genome sequence was announced in June 2000, with analyses published in February 2001. Although we are still at the early stages of extracting scientific benefit from this scientific achievement, it is already clear, that it will make an enormous contribution to our understanding of human biology and of medicine. Our increasing scientific understanding of human molecular genetics will benefit the field of gene therapy, which, I believe, has reached a critical phase.

In 2000, Cavazzano-Calvo et al reported the successful use gene therapy to treat two infants with the X-linked form of severe combined immune deficiency (X-SCID), the first gene therapy cure of an inherited disorder. The French Group now have treated eleven patients. Unfortunately, two patients subsequently developed a leukaemia-like disease, the first case being reported in September 2002. In both patients, the retrovirus had inserted into an intron of the LMO-2 gene on chromosome 11. It has been know that LMO-2, an oncogene, plays a role in some forms of childhood leukaemia. Insertional mutagenesis always has been recognized as a theoretical complication of using retroviruses as vectors for gene therapy but this is the first time it has been observed in man.

The success achieved by the French Group in treating infants with X-SCID with gene therapy must not be overlooked. However, such trials must proceed with caution. Only by doing so can we ensure that gene therapy can make the difficult transition from being a laboratory experiment to being a clinical reality.

Here in the UK, doctors at Great Ormond Street Hospital for Sick Children have used a similar gene therapy approach to treat five patients with X-SCID. All these patients are progressing well and none show any sign of leukaemia.

GTAC considered the implications of the leukaemia cases for UK patients and decided that in balancing the risks and benefits to infants with X-SCID and in weighing-up the option of alternative treatments, it would be unethical to withdraw GTAC approval of the UK X-SCID study. However, it was agreed that recruitment into these trials should only be on a case-by-case basis, assessing the eligibility of each patient in the light of the most up-to-date information. In addition, it was decided to establish in association with the Committee for the Safety of Medicines, an expert working group to review the UK trials using retroviruses with a remit to make recommendations on the use of these vectors in gene therapy.

I wish to thank the scientific community for their contributions to GTAC in responding to our numerous requests. It is most reassuring to know that the scientists and doctors can work together and respond appropriately to any problems that may arise in the course of clinical gene therapy.

The European Directive on Clinical Trials will greatly influence the conduct of research in the future. With the translation of the Directive into national legislation, a new UK Ethics Committee Authority (UKECA) will be established with responsibilities for establishing, recognising and monitoring research ethics committees. It has been agreed that UKECA will recognise GTAC as the UK research ethics committee for all gene therapy trials under the new legislation.

During the year the Committee said farewell to three members, Professor Ian Hart, Mrs Anne Hunt and Mrs Rosemary Barnes. I wish to record my thanks to these members for their invaluable contribution to GTAC.

Professor Norman Nevin
Chairman of GTAC
April 2003

SECTION 1: PROTOCOLS REVIEWED BY GTAC IN 2002

GTAC reviewed the followong proposals in 2002. Three proposals reviewed during 2001 were granted full approval (section 2). The committee received a total of thirty-nine applications to amend ongoing protocols (Annex G). No notifications were received during the reporting year.

EPSTEIN-BARR VIRUS (EBV) INFECTION

Epstein-Barr Virus (EBV) is a herpes virus that shows affinity for infection of B-cells (antibody-producing cells) of the immune system. EBV infection is extremely common throughout the world. About 95% of adults have antibodies in their blood against EBV, showing that they have been infected at some time by the virus. Infection often occurs during childhood without significant or obvious symptoms. During adolescence or young adulthood, infection with EBV can result in *infectious mononucleosis* (glandular fever) which leads to fever, sore throat, swollen lymph glands and fatigue. Afterwards, EBV will remain dormant in a reservoir of cells for the rest of the patient's life. Patients with suppressed immune systems, such as those with HIV or recipients of transplants, seem particularly susceptible to EBV infection.

In certain instances, EBV infection is associated with a number of cancers including proportions of Hodgkin's disease, Burkitt's lymphoma, and post-lymphoproliferative disease. EBV is also implicated in nasopharyngeal carcinoma (NPC), which is one of the most common cancers in South-East Asia. In all of these cases, viral material can be detected in malignant cells. An important factor in the development of EBV-positive malignancy seems to depend on the repertoire of viral proteins being produced in the infected cells.

When EBV infects the B-cells of healthy individuals a number of proteins (or antigens) are produced by the virus, including EBNA 1, 2, 3A, 3B, 3C and LMP 1 and 2. These are recognised by a variety of components of the immune system, the net result of which is the purging and control of EBV-positive cells. There are two crucial white blood cell types involved in this immune response. One is called a Cytotoxic T lymphocytes (CTL) which recognises and kills cells producing EBNA 3A, 3B and 3C proteins and (less effectively) LMP2. Another type of white blood cell, called a T helper cell, recognises the EBNA1 protein. These T-helper cells facilitate the immune system to attack and eliminate these cells.

In EBV-positive cancers, some viral proteins (or antigens) are not present in malignant cells. For example, only EBNA 1 is seen in EBV-positive cells from Burkitt's Lymphoma whilst in Nasopharnygeal carcinoma, only EBNA 1 and LMP 2 can be reliably detected. However, EBNA 1 and LMP 2 can be normally be observed in almost all EBV-positive malignancies.

GTAC 066: Recombinant Modified Vaccinia Ankara (MVA)-based vaccine encoding Epstein Barr Virus target antigens; phase I dose escalation trial to determine immunogenicity and toxicity in patients with EBV+ malignancy. Institute for Cancer Studies, University of Birmingham.

In this study a recombinant viral vaccine will be injected into the skin of patients with EBV positive cancers. The virus (MVA) has been modified to produce a protein containing

portions of both EBNA1 and LMP2, which will be fused together (MVA-EBNA1/LMP2). It is hoped that the protein from this vaccine will induce both CTL's and T helper cells of the patients' immune system to recognise these EBV proteins in malignant cells and consequently eliminate those cells. Approval was granted in February 2002 on the condition that minor changes were made to the patient information leaflet.

CYTOMEGALOVIRUS (CMV) INFECTION

Human cytomegalovirus (CMV) is a member of the Herpes family of viruses that include Herpes Simplex (causing cold sores), varicella-zoster (causing chickenpox) and Epstein-Barr virus (causing glandular fever) and is one of the largest and most complex of the viruses. The vast majority of adults have been infected with CMV during their childhood, adolescence or early adult life, but without significant medical consequence. This is because, in healthy individuals, the immune system produces a cellular response against the virus which keeps infection at bay for life. In particular, Cytotoxic T lymphocytes (CTL's) and T-helper cells mediate this response. Despite immune system control of infection however, the virus remains within the body, in lymph nodes, spleen and other tissues, in a dormant state.

Should a person's cellular immune system become compromised, as a consequence HIV infection for example, CMV can lead to serious medical complications either when challenged by a new CMV infection or by reactivation of a dormant infection. Symptoms can include severe respiratory problems (pneumonia), lesions and perforation of the gut, damage to the retina and even brain inflammation.

In haemopoietic stem cell transplantation (HSCT; bone marrow transplantation), the patients first receive chemotherapy alone or in combination with radiotherapy to prevent subsequent rejection on the donor's marrow cells. In addition, to prevent Graft Versus Host Disease (GvHD), where the donated marrow may mount an immune attack on the recipients' own cells, recipients are routinely given immunosuppressive agents. Once the transplant has taken place and the marrow engrafts, it can take the immune system several months to reconstitute itself in the recipient. All of this leaves bone marrow recipients susceptible to opportunistic infections, which commonly include CMV infections. Likewise, solid organ (e.g. kidney) transplant patients face similar problems with immunosuppression and opportunistic infections. Currently, there is no effective treatment for CMV infection.

GTAC069: A phase I/II study of vaccination with a DNA fusion gene containing an epitope of CMV in allograft donors and patients awaiting renal transplantation. University of Southampton.

This study involves a DNA vaccine which it is hoped will enhance an immune response against CMV in transplant recipients. In bone marrow donors or kidney patients awaiting transplant, it is hoped that a DNA plasmid (non-viral gene delivery vehicle) will drive production of a immuno-stimulatory portion (antigen) of one of the major CMV proteins called pp65. By injecting this DNA directly into patients' muscles, it is hoped that the DNA will be taken up by certain cells of the immune system, Antigen Presenting Cells (APC's), where it will be converted to pp65 protein. Another protein, unrelated to CMV, called Tetanus Toxin is particularly adept at stimulating the immune system. The researchers have "fused" a small portion of this protein to pp65 in the hope that the overall immune response to the "fusion protein" and consequently CMV will be even more powerful.

It is hoped that these "primed" APC's will enhance the ability of the CTL's to recognise and destroy CMV itself or any cells containing pp65.

If successful, this approach could be used to enhance the bone marrow donor's ability to fight CMV infection. Bone marrow itself contains CTL's and their precursors, and immunity against CMV could potentially be transferred from donor to patient during the transplant. Similarly, injection of the DNA into kidney patients pre-transplant might augment their ability to attack any CMV infection that might occur when immunosuppressed.

The committee recommended that the study be separated into two individual protocols. Formal approval for the vaccination of allograft donors and recipients was granted in June 2002. The researchers were invited to submit a new protocol relating to the vaccination of renal transplant patients.

METASTATIC MELANOMA

Malignant melanoma (or skin cancer) has been increasing in prevalence over the past two decades. As awareness has increased more patients have been diagnosed at an early, surgically-curable stage. Chemotherapy can help alleviate symptoms for patients with advanced disease but a significant overall effect on survival has not been demonstrated for patients with metastatic disease. There is evidence that melanoma patients can mount an immune response to the disease. This is because certain molecules (antigens) found on the surface of cancerous melanoma cells are unique to those cancers and therefore recognised as "non-self" by the immune system.

GTAC 071: Phase I/II study to determine the optimum dose and dosing regimen then to assess the efficacy of a poly-epitope pharmaccine (therapeutic vaccine), involving pSG2.Mel3 and MVA.Mel3, in patients with Stage III or Stage IV metastatic melanoma. University of Manchester.

This study is a follow-up to a previous study in patients with malignant melanoma. This study uses a vaccination strategy to further stimulate an immune response against cancerous skin cells. Two vaccines are proposed for use in this study, one a DNA vaccine (*pSG2.Mel3*) and the other, a Modified Vaccinia Ankara (*MVA.Mel3*). Each proposed vaccine contains seven melanoma gene sequences (*Mel3*) which code for antigens that have been shown to induce an immune response in humans. The use of a combination of DNA vaccine and MVA vaccine is thought to elicit a greater immune response than either alone in a procedure that is referred to as a "prime-boost" strategy.

Both vaccines have been well tolerated in a previous phase I study in melanoma patients. The researchers now wished to optimise any immunological responses generated by the vaccines and determine the optimal dosing regimen. The study was granted conditional approval subject to a number of changes to the protocol and patient information. Full approval was granted in September 2002.

ADENOSINE DEAMINASE DEFICIENCY

Severe Combined Immune Deficiency (SCID) is the name given to a collection of genetic diseases of the immune system. Symptoms typically include susceptibility to a range of infections from viruses, bacteria and fungi, caused by a failure of the immune system to develop properly. SCID can vary in severity, but typically patients are diagnosed in the first two years of life and are likely to die without treatment.

ADA-SCID can affect both boys and girls. ADA stands for adenosine deaminase, a metabolic enzyme that is important for, amongst other things, DNA synthesis. The gene encoding the ADA enzyme is on chromosome 20. In ADA-SCID patients, both parental copies of chromosome 20 contain faulty versions of the ADA gene. The ADA enzyme is normally present in all cells of the body. In ADA-SCID patients, loss of ADA hampers development and function of progenitor cells of the immune system called the lymphoid cells. These cells would normally develop into and T-lymphocytes that attack virally-infected and cancer cells and B-lymphocytes that produce antibodies to fight infection. As ADA-SCID patients have only limited numbers of these cells, they have an impaired ability to fight infection.

The most successful approach to treat ADA-SCID patients involves bone marrow transplant from a related or compatible donor. Typically, this results in immune system function about 90% of the time, but compatible donors are available in only about 30% of cases. Where only limited-match donors are available, bone marrow transplant is unsuccessful in about two thirds of cases. Bone marrow transplants can be complicated by Graft versus Host disease, where transplanted immune system cells attack the recipient patient's own tissues. An alternative option, not curative however, is known as enzyme replacement therapy. Here, the ADA enzyme is linked with a chemical called PEG (PEG-ADA) and is normally administered weekly. This provides about 80% of patients with some functional enzyme.

In 1990 ADA-SCID was the first genetic condition where gene therapy was attempted and since then there have been a number of trials. Efficacy has been limited, it is believed for two reasons. Firstly, patients were maintained on PEG-ADA during and after the gene therapy. It is believed that any survival advantage conferred on a gene-modified cell would effectively be masked by co-treatment of diseased cells with PEG-ADA and immune system constitution would be inhibited. Secondly, it has been proposed that giving patients mild chemotherapy prior to re-infusing gene-modified cells should kill off "diseased", unmodifed lymphoid cells and offer further selective growth advantage to the gene-modified cells. This procedure is known as *non-myeloablative conditioning*.

GTAC 072: Phase I clinical gene therapy protocol for adenosine deaminase deficiency. Great Ormond Street Hospital, London.

In the present study, the researchers will use a novel retroviral vector to deliver the normal version of the ADA gene to bone marrow cells from five ADA-SCID patients. Patients are likely to be under two years of age, will receive non-myeloblative chemotherapy to condition their cells and will not receive PEG-ADA prior to or during the trial. Patients will not have a suitable bone marrow donor or will have unsuccessful immune system recovery from previous bone marrow transplantation. Patients will not receive PEG-ADA if newly diagnosed or will be taken off PEG-ADA treatment 4–6 weeks prior to gene therapy. The study was approved in December 2002 subject to minor amendments, including changes to the patient information leaflet.

SECTION 2: CHAIRMAN'S ACTIONS

Final approval was granted by Chairman's Action (in accordance with the provision set out for their conditional approval) to three studies which had been originally reviewed by the committee during 2001:

GTAC 064: A phase I/II trial of intravenous vs hepatic arterial infusion of an E1A-CR2 deleted adenovirus in patients with inoperable, metastatic colorectal carcinoma (February 2002).

GTAC 065: A phase I trial of polyMEL, a polyepitope DNA vaccine in the treatment of metastatic melanoma (January 2002).

GTAC 068: A phase I trial of HER2neu – a polyepitope DNA vaccine encoding HER-2 epitopes in the treatment of breast cancer (January 2002).

These studies are detailed in GTAC's 8th Annual report.

SECTION 3: REGULATORY ISSUES

LEUKAEMIA LINKED TO GENE THERAPY TREATMENT FOR X-SCID

On 16 September 2002 GTAC was notified that a child enrolled in a French X-SCID gene therapy trial had developed leukaemia (a type of cancer). GTAC immediately contacted both the French researchers and the French authorities to obtain further details and the agenda for GTAC's 39th meeting on 2nd October was cleared in order to consider the implications of this SAE as an emergency item. Details of UK studies were reviewed, particularly in relation to route of administration, the nature of the viral payload and patient group. Two UK studies involving the treatment of children with retroviral vectors were identified as closely related to the French. The UK principal investigator confirmed that no patient would be treated pending the outcome of GTAC's discussions.

In its original review of these studies, GTAC had recognised the possibility of cancer occurring as a result of the insertion of the vector into the genetic material of the cell. GTAC is satisfied that all parents of children treated in the UK were informed of this risk and received appropriate counselling prior to treatment. GTAC stipulated that in the light of the case of leukaemia all UK retroviral studies should specifically inform and counsel patients in relation to the risk of gene disruption and therefore cancer.

In issuing their recommendations on 4th October 2002, GTAC stressed that the successful X-SCID studies represent a significant milestone in the development of gene therapy treatments. GTAC recommended:

- On a case by case basis, GTAC will review developments before approving entry of any new patient to the UK studies.
- Families with children eligible to enter the trials will be fully counselled about this new development so that their choice of treatment can be as informed as possible.
- A specialised sub-committee would be established to issue further detailed advice to the Department of Health and the gene therapy community as appropriate. The sub-committee, scheduled to meet on 11 March will be a joint working party of GTAC and the Committee on Safety of Medicines (CSM). They will issue their recommendations to the Department of Health and the Medicines Control Agency.

BACKGROUND TO X-SCID GENE THERAPY

In the immune system, cells known as lymphocytes have a variety of functions including the production of antibodies and acting to prevent viral, bacterial and fungal infections. In X-SCID a defect in the common gamma c (or γc) gene on the X-chromosome results in the failure of lymphocytes to develop and function properly.

X-SCID affects boys, with an estimated frequency of 1 in 50,000 to 100,000 births. There are 3 or 4 newly diagnosed cases each year in the UK. Without treatment, boys would normally die in their first year. Until recently, bone marrow transplantation, or more specifically haematopoetic stem cell transplantation (HSCT), offered the only curative option for the

treatment of X-SCID. Where a fully matched donor is available, HSCT has a survival rate of about 90%. However, a matched donor is available in about a third of cases.

For patients where only partially matched donors are available, the survival rates range from 53% to 79%. Contributions to mortality come from the toxic effects of chemotherapy and Graft versus Host Disease (GvHD), where the introduced donor's cells recognise the patient's cells as foreign and mount an immune attack on the patient's tissues.

For patients where no fully matched donor is available, new treatment options are being actively explored, in particular with long-term correction of the underlying genetic defect via retroviral gene therapy.

In the X-SCID gene therapy protocol, bone marrow is taken from the patient. In the laboratory, stem cells are purified from this bone marrow and then infected with the retrovirus carrying a normal copy of the gc gene. The retrovirally-infected cells are then put back into the patient. Because the viral manipulation of the cells takes place outside the body, the process is referred to as ex vivo gene therapy.

The first results indicating the success of gc gene replacement using retroviral gene therapy for the treatment of X-SCID were reported in Science in April 2000 by Dr. Fischer in France. In that report, two patients showed immune system reconstitution following the gene therapy.

Because retroviruses insert their genetic material randomly into the host genome there is a possibility that insertion might result in the activation of an oncogene or inactivation of a tumour suppresser gene. Either of these events could lead to the eventual transformation of a cell into a cancer cell. It is known that replication-competent virus (RCR) can cause lymphomas in severely immunocompromised primates. For this reason batches of gene therapy vector must be stringently tested for the presence of contamination with RCR.

The plight of children with X-SCID first captured the public imagination following media publicity surrounding an American child, David Vetter, dubbed *"the boy in the bubble"*. Because David's elder brother had died of SCID before he was born, the medical profession was alerted to the possibility he would have the disorder and David was transferred to a sterile environment after birth to await a bone marrow transplant. He lived for 12 years physically isolated in a plastic sterile environment, and venturing outside only in a NASA designed sterile space suit. David died in 1983, before his 13th birthday following an unsuccessful bone marrow transplant. Alternative treatments for children like David are still desperately needed.

GTAC POSITION ON THE USE OF RETROVIRAL VECTORS CONTAINING THE ΔLNGFR TRANSGENE

In June 2002 concern was raised by a preclinical study, published by Li *et al* [1] which demonstrated disruption of an oncogene by a retroviral vector carrying an insert called ΔLNGFR. The insert is used because it "marks" the surface of cells which have successfully taken up the gene therapy vector. Where the cells are treated *in vitro* this allows the researchers to sort and return to the patient the successfully treated cells.

[1] Li *et al* – see p.12

The committee considered the available evidence and its implications for clinical gene therapy in general and for trials approved by GTAC in particular. In June 2002 GTAC reached the following conclusions:

SUMMARY OF GTAC CONCLUSIONS IN RELATION TO RISKS ASSOCIATED WITH RETROVIRAL VECTORS CARRYING ΔLNGFR

The published study of Li *et al.*[1] provides further support to the notion that retroviral vectors can cause oncogenic transformation under certain circumstances. In this study, the retrovirus carrying a truncated form of the LNGFR gene (Δ*LNGFR*) disrupted a gene called *Evi*1. The exact risk, however, remains unquantified. The study in question, using a vector derived from Moloney Murine Leukemia virus encoding a truncated version of LNGRF, reported that a clonally-expanded population of bone marrow cells in irradiated secondary and tertiary mouse recipients caused leukaemia. In addition to the disruption of *Evi*1 gene expression caused by retroviral integration, the ΔLNGFR transgenic product is itself likely to have participated in the transformation event, most likely, by interference with NGF signalling.

In determining whether it is appropriate to proceed with clinical trials using this type of vector, an important consideration rests on the context and target cell population of the study. The use of such a retroviral vector for the treatment of chronic diseases, such as primary immuno-deficiencies in children would seem unwise, as would the targeted transduction of cells known to be NGF responsive.

Currently, GTAC has reviewed and approved the use of this type of vector for the transduction of T-cells following bone marrow transplantation in the management of Graft versus Host Disease (GvHD). Although T-cells may have tyrosine kinase receptor function in some circumstances, in GvHD protocols the vast majority of transduced cells could be eliminated via the action of a thymidine kinase "suicide gene" on ganciclovir. Additionally, the potential benefit for transplantation patients seems to outweigh the risks.

For these GvHD studies, GTAC suggests that investigators extend the monitoring of recipients' peripheral T-cells to include analysis of clonality with respect to vector integration. If there is evidence of an emerging clone with a simple integration pattern, then ganciclovir rescue should be considered. Also, in the light of published studies, it would be helpful to know whether vector transduction of normal T-cells leads to NGF-responsive growth. A positive result would favour switching to an alternative vector for future

[1] Li et al. Murine leukaemia induced by retroviral gene marking. Science, 2002. volume 296. 497

SECTION 4: GTAC WORKSHOP – GENE THERAPY & CANCER

ROYAL COLLEGE OF PHYSICIANS, LONDON 4TH MARCH 2002

The GTAC public meeting for 2002 focused on gene therapy approaches to the treatment of cancer. Those present included interested members of the public, patient groups, research nursing staff, academics and members of industry. The meeting was chaired by Professor David Harrison and the opening address was given by Professor Norman Nevin.

Early predictions suggested that gene therapy would be studied in the context of single gene disorders like Cystic Fibrosis. However, over the past ten years the majority of gene therapy trials have involved the cancers. This is perhaps because cancer patients represent a large population, often with life-threatening conditions where conventional treatment options are exhausted. In addition, increased understanding of the biology of cancer has suggested new ways to treat the disease using molecular approaches. Cancer also represents a broad range of diseases and its treatment involves a wide variety of approaches, from the use of oncolytic viruses to immunotherapy.

Obstacles that lie in the way of effective gene therapies for cancer include the lack of a truly efficient gene delivery system and problems with maintenance of gene expression. However, over the last decade, knowledge gained of basic biology and from clinical experience is likely to strengthen our treatments for cancer, including the use of gene therapy.

The meeting also included presentations from Professor T. Hamblin, who spoke on genetic vaccination strategies for leukemia and lymphoma; Dr. David Kirn, who spoke on clinical encounters with conditionally replicating viruses in the treatment of cancer; Professor Moira Brown, who spoke on the use of a Herpes Simplex Virus mutant in glioma and melanoma patients; Professor Martin Gore (Royal Marsden Hospital, London), who outlined the ethical and practical issues for gene therapy clinical trials and Professor David Kerr (Radcliffe Infirmary, University of Oxford) who gave an account of his team's experiences using Adenoviral vectors in the treatment of Liver Cancer. (Biographies and abstracts from these presentations are provided below.)

Following on from the speaker's presentations, there was an open discussion, with questioning thrown open to the floor. Discussion events like this were considered vital to teasing out regulatory and safety issues for gene therapy, such as the use of antibiotic resistance genes in DNA plasmids.

The balance of science versus ethics was next considered. Although separate issues in some cases, it was suggested that if the science was good then, in general, the ethics would be good, particularly when the research was to be carried out by a multidisciplinary team.

The level of animal experimentation required prior to clinical study was also addressed. It was noted that there were both financial and ethical constraints on animal studies. A distinction was made between animal experiments designed to examine efficacy of a study agent and those which attempted to measure toxicity. In the former case, some experiments might be considered unnecessary and uninformative. In the latter case, however, it was

agreed that having some feel for toxicity in animals was highly valuable before proceeding to human trials.

Finally, issues surrounding informed consent were discussed. It was suggested that truly informed consent might not be really possible. In many instances, patient information sheets could be viewed as too long and complex. However, it was suggested that many cancer patients are willing to take decisions involving risk without appropriate reference to the patient information. An independent counsellor was proposed as useful way to help patients decide whether or not to participate in any research trial.

SPEAKERS' BIOGRAPHIES

Professor Norman C. Nevin BSc MD FFPHM FRCPath FRCPed FRCP GTAC Chairman

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

Professor Terry Hamblin, Southampton University & Royal Bournemouth Hospital

Professor Hamblin graduated from Bristol University Medical School in 1967. Following junior doctor training in Bristol he attained membership of the Royal College of Physicians and Royal College of Pathologists and was appointed as Consultant Haematologist in Bournemouth in 1974. From there he began a long collaboration with the Tenovus Research Laboratory at Southampton University. He was given a personal chair in Immunohaematology at Southampton in 1985.

His research interest has been in immunotherapy of leukaemias and lymphoma on which he has published four books, 30 chapters and over 300 scientific articles. His most significant finding has been the separation of chronic lymphocytic leukaemia into two diseases of widely differing prognoses based on the sequencing of their immunoglobulin genes. He is currently coordinator of four clinical trials of DNA vaccination in haematological malignancies.

He is also chairman of the UK Chronic Lymphocytic Leukaemia Forum, a Council Member of the Research Defence Society and a member of GTAC.

Dr. David Kirn, Hammersmith Hospital, London

David Kirn is currently Director and founder of the Viral and Genetic Therapy Programme for the Imperial Cancer Research Fund (Cancer Research U.K.), located at the Hammersmith Hospital in London. He is also Senior Lecturer and Hon. Consultant at the Imperial College School of Medicine, and Visiting Professor (Haddow Fellowship) at the Royal Marsden Hospital and Institute for Cancer Research in London. He also spent five years with a biotechnology company as Vice President in charge of Clinical Research and preclinical

research on novel therapies for cancer. He has over fifty peer-reviewed publications and book chapters, and he is on the editorial review board of seven different medical and scientific journals and is board-certified in Internal Medicine and Medical Oncology.

He received his undergraduate degree in 1985 from the University of California, Berkeley where he received the Departmental Citation for Physiology and membership into the Phi Beta Kappa honor society. He received his M.D. in 1989 from the University of California, San Francisco after graduating with honors and membership in the Alpha Omega Alpha medical honor society. He then completed internal medicine residency training in 1992 as a Clinical Fellow in Internal Medicine at Harvard Medical School based at the Brigham and Women's Hospital in Boston, MA. During his third year of residency training he was elected Chief Medical Resident at the West Roxbury V.A. Hospital, a Harvard affiliated teaching hospital. He subsequently completed his Hematology-Oncology Fellowship at the University of California, San Francisco. Following completion he became Assistant Professor (adjunct) at the University of California, San Francisco.

Professor S. Moira Brown BSc, PhD, FRCPath, FRSE University of Glasgow

Moira Brown is Professor of Neurovirology in the Department of Neurology of the University of Glasgow. She works at the Institute of Neurological Sciences at the Southern General Hospital, Glasgow. For most of her working life she was employed by the UK Medical Research Council on the staff of their Virology Unit. In 1995, she transferred to the University of Glasgow with the express aim of translating her research to the clinic.

She has worked on Herpes simplex virus since her post graduate days and has been at the forefront internationally of HSV genetics, latency and pathogenesis over many years. Her research led to the first isolation of avirulent HSV mutants. The finding that these mutants could replicate exponentially in actively dividing cells, highlighted their potential in cancer therapy.

She has pushed forward the introduction of oncolytic herpes simplex virus into the clinic and has been instrumental in establishing the credibility of this approach in the potential control of cancer. She is the Chief Scientist and a director of Crusade Laboratories Ltd. Professor Brown is Chairperson of the Scottish Hospital Endowments Research Trust (SHERT) and is a Fellow of The Royal Society of Edinburgh.

Professor Martin Gore MB, BS (Lond) PhD (London) MRCP (UK) Royal Marsden Hospital, London

Martin Gore is a consultant cancer physician at the Royal Marsden Hospital, Honorary Senior Lecturer and Member of Faculty at the Institute of Cancer Research, London and Honorary Consultant at Epsom District Hospital in Surrey. He has been involved in clinical cancer research for over twenty years and specifically in gene therapy since the early 1990s. He is chairman of the NCRI melanoma group, the MRC Renal Cell Cancer Trial and UK melanoma study group guidelines committee. He is a serving member on GTAC.

Martin has produced over 200 publications on his area of research, including review articles and book chapters. He is on the editorial boards of several medical journals including *Journal of Clinical Oncology, Gynecologic Oncology* and *Melanoma Research*.

David J Kerr MD, DSc, FRCP (Glasgow and London) FmedSci CBE Professor of Clinical Oncology, University of Oxford

David Kerr is Rhodes Professor of Therapeutics and Clinical Pharmacology at the University of Oxford and Director of the National Translational Cancer Research Network. He is working with colleagues in Oxford to build a new Institute for Cancer Medicine. Immediately prior to this new appointment he had been the Professor of Clinical Oncology in Birmingham between 1992–2001 and had been instrumental in establishing the new Institute of Cancer Studies at the University of Birmingham, which has a research staff of around two hundred clinical and basic scientists. He has an international reputation for treatment of and research into colorectal cancer and he is developing new approaches to cancer treatment which involve gene therapy. The quality of his work has been recognised by the award of several international prizes, and the first Nye-Bevan award for innovation; he has published more than 200 articles in peer-reviewed journals and has contributed to many books on cancer. He is a member of the National Cancer Taskforce, the Commission for Health Improvement, chairs the Cancer Services Collaborative, a leading cancer pathway re-design project, and is Editor-in-Chief of Annals of Oncology, Europe's premier medical oncology journal.

PRESENTATIONS

Professor Terry Hamblin, Southampton University & Royal Bournemouth Hospital

Gene Therapy in Leukaemia and Lymphoma

The molecular mechanisms involved in the development of most haematological tumours are now understood. Gene transfer represents one approach to influencing these tumours. Because bone marrow stem cells can be harvested from the body, manipulated in the laboratory and then returned to the patient, the management of leukaemia and lymphoma has been one of the key target areas for gene therapy. Therapy has been directed at replacing damaged tumour suppressor genes, or blocking hyperactive oncogenes or introducing targeted suicide genes. Most systems require specially engineered viruses to deliver the gene, and there are problems arising from how to transfect sufficient tumour cells, how to exploit any bystander effects by which non-transfected tumour cells may be eliminated and how to avoid an immune response to the viral vector or newly expressed proteins.

A different approach is to use gene transfer to effect immunological rejection of the tumour. Here, we start with a handicap in that the tumour has already evaded any existing immunological surveillance, and as haematological tumours are in essence tumours of the immune system, we may assume that the immune system is to some degree damaged. Furthermore, standard therapy for these tumours, chemotherapy and radiotherapy is itself immunosuppressive.

Our approach has been to target idiotype, which acts as a tumour-specific target for all tumours of B-lymphocytes. We know that an immune response against idiotype is capable of successfully destroying B cell lymphomas, but, because every idiotype is different, the task of making tailor-made vaccines for each patient is beyond the resources of all but the exceedingly rich. We have demonstrated that this task can be overcome by making DNA vaccines. Native DNA coding for idiotype injected into muscle is processed so as to act as a specific vaccine that produces long term immunity against the patient's own lymphoma. Unfortunately, idiotype, like most tumour antigens, is a weak immunogen. We have found

that we can boost the immune response by coupling the idiotype gene to a gene coding for part of the tetanus toxin molecule. It works by alerting an immune system designed to react to bacterial, rather than tumour, products and by using T helper cells already primed to react to tetanus.

DNA vaccines contain immunostimulatory sequences that stimulate the release of cytokines that an immune response biased towards cytotoxic T cells. Such a response is necessary to attack intracellular rather than surface targets. Most potential tumour targets are intracellular, so this approach is likely to have applications against a wide range of tumours, not simply leukaemias and lymphomas. Clinical trials against lymphoma, chronic lymphatic leukaemia and myeloma have begun with promising early results.

David Kirn. Viral and Gene Therapy Program, Imperial Cancer Research Fund, Molecular Oncology Unit, Hammersmith Hospital, London, UK

Systemic administration of replication-selective adenoviruses

Replication-selective viruses and bacteria are being developed for the treatment of cancer. dl1520 (Onyx 015 or CI-1042, Pfizer) is an E1B-55kD gene-deleted replication-selective adenovirus[1–4] that was the first genetically-engineered, replication-selective virus to enter trials in humans. We used a staged clinical development approach that proceeded from intratumoral (i.t.) to intraperitoneal (i.p.), intra-arterial (i.a.) and eventually intravenous (i.v.) administration. Over 230 cancer patients have been treated to date, including 174 i.t. (head and neck, pancreatic, GI met. to liver), 16 i.p. (ovarian), 31 i.a. (hepatic artery for colorectal metastases to liver), 10 i.v. (lung metastases, any carcinoma). dl1520 has been well-tolerated by all routes of administration, including doses of up to $2x10^{12}$ particles i.a. and $2x10^{13}$ particles i.v.. Common toxicities included fever (typically grade 2–3 i.a./i.v.), asthenia and injection site pain (i.t.). Clinically-relevant hepatotoxicity due to dl1520 was not demonstrated, although transient grade 1-2 transaminitis was documented in some patients following i.v. infusion at doses >2x1012 particles. Reproducible evidence of viral replication was obtained (within <10 days) following 1) i.t., i.a. and i.v. administration, 2) in head and neck and colorectal cancer patients but not in pancreatic (i.t.) or ovarian (i.p.) carcinomas; no patient had replication documented >10 days after treatment. Single agent-induced objective tumor regressions were demonstrated in head and neck cancers (15–20%) but not in pancreatic, colorectal, ovarian or metastatic lung tumors. Evidence for potential synergy with chemotherapy has been obtained from head and neck (i.t.) and colorectal cancer patients (i.a.)[5] [6]. IL-1, IL-6, IL-10, interferon-gamma and TNF levels all increased acutely following i.a. and/or i.v. administration[6] [7].

[1] Barker, D. D. and Berk, A. J., Adenovirus proteins from both E1B reading frames are required for transformation of rodent cells by viral infection and DNA transfection, Virology. 156: 107–121, 1987.
[2] Bischoff, J. R., Kirn, D. H., Williams, A., Heise, C., Horn, S., Muna, M., Ng, L., Nye, J. A., Sampson-Johannes, A., Fattaey, A., and McCormick, F. An adenovirus mutant that replicates selectively in p53-deficient human tumor cells, Science. 274: 373–376, 1996.
[3] Heise, C., Sampson, J. A., Williams, A., McCormick, F., Von Hoff, D. and Kirn, D. H. ONYX-015, an E1B gene-attenuated adenovirus, causes tumor-specific cytolysis and antitumoral efficacy that can be augmented by standard chemotherapeutic agents, Nat Med. 3: 639–45, 1997.
[4] Harada, J. and Berk, A., p53-independent and -dependent requirements for E1B-55kD in adenovirus type 5 replication, J. Virology. 73: 5333–5344, 1999.
[5] Khuri, F., Nemunaitis, J. Ganly, I., Arseneau, J., Gore, M., Ironside, J., Heise, C., Romel, L., Kaye, S., and, Kirn D. A controlled trial of ONYX-015, a selectively-replicating adenovirus, in combination with cisplatin and 5-fluorouracil in patients with recurrent head and neck cancer, Nature Medicine, 2000.
[6] Reid, A., Galanis, E., Abbruzzese, J., Romel, L., Rubin, J., and Kirn, D., A phase I/II trial of ONYX-015 administered by hepatic artery infusion to patients with colorectal carcinoma, Am Soc Clin Oncol, 2000.
[7] Nemunaitis J, Cunningham C, Maples P, Buchanan A, Blackburn A, Romel L, Kirn D. A phase I trial of intravenous administration with an E1B-55kD gene-deleted adenovirus Onyx-015 in patients with cancer metastatic to the lung. Am Soc Clin Oncol 2000.

Given the clear documentation of safety and feasibility with this approach following intravascular administration, but the lack of significant single agent efficacy to date with dl1520, we carried out preclinical studies of intravenous treatment with a significantly more potent adenovirus dl922/947 (E1A mutant) in nude mouse-human tumour xenograft models; antitumoral efficacy was significantly superior to dl1520 in all models, and equivalent to or even superior to wildtype adenovirus i.v. The replication-selective virus approach has promise as a systemic treatment for cancer.

Acknowledgements: Invaluable contributions were made by Margaret Uprichard, John Nemunaitis, Tony Reid Carla Heise and Fadlo Khuri, among many others including the patients themselves.

Professor Moira Brown. University of Glasgow

Herpes simplex virus HSV1716 in cancer therapy

This presentation will cover the properties of the virus *in vitro* and *in vivo* and its molecular characterisation and preclinical development in a range of tumour models. Clinical experience in the use of the virus in Phase 1 trials will be covered in full. These trials include patients with primary and recurrent glioma, metastatic melanoma and squamous cell cancer of the head and neck.

In addition, the strategy employed to combine the oncolytic potential of HSV1716 with chemotherapy and targeted radiotherapy will be discussed.

Professor Martin Gore. The Royal Marsden Hospital, London

Gene Therapy with Autologous Interleukin 2-Secreting Tumour Cells in Patients with Malignant Melanoma

We vaccinated metastatic melanoma patients with irradiated, autologous melanoma cells genetically engineered to secrete interleukin 2 (IL-2) to investigate whether an anti-tumour immune response would be induced. Melanoma cell cultures were established from surgical specimens and were engineered to secrete IL-2 by infection with recombinant retrovirus. Twelve patients were vaccinated subcutaneously one, two, or three times with approximately 107 irradiated, autologous, IL-2-secreting tumour cells. Forty-one patients were considered potential candidates for the trial and had melanoma cells harvested for this purpose. The main reason for a failure to vaccinate patients was rapid progression of disease between harvest and vaccine preparation. Treatment was well tolerated with local reactions at 11 of 24 injection sites and minor systemic symptoms of fever and headache after 6 injections. One patient developed anti-tumour DTH after the first vaccination and showed an increased response after the second vaccination. Anti-autologous tumour CTLs could be detected prevaccination in the peripheral blood of seven patients and their activity increased after vaccination in four patients. No UICC-defined clinical responses were seen, but three patients had stable disease for 7–15 months, one of whom has not yet progressed (15+ months). Thus, patient vaccination with autologous, genetically engineered tumour cells is feasible and safe. Anti-tumour DTH and CTLs can be induced in some patients with such a vaccine[8].

[8] Palmer K, Moore J, Everard M, Harris J.D, Rodgers S, Rees R.C, Murray A.K, Mascarir R, Kirkwood J, Riches P.G, Fisher C, Thomas J.M, Harries M, Johnston S.R.D, Collins M.K.L, Gore M.E. Human Gene Therapy, 1999; 10: 1261–1268

Professor David Kerr, Radcliffe Infirmary, University of Oxford

Gene therapy for Liver Cancer

The liver is a common site for metastasis or spread, especially from primary cancers of the bowel and breast. Although chemotherapy can slow the growth of the cancer it cannot eradicate it, therefore new treatments are vital. Similarly, primary cancer of the liver is rare in the UK but world-wide, given its association with Hepatitis B/C, it is a common cancer which is resistant to most forms of conventional chemotherapy.

Virus Directed Enzyme Prodrug Therapy (VDEPT), depends on Adenoviral delivery of the gene coding for a enzyme (nitroimidazole reductase) which can convert an inactive, non-toxic prodrug, (CB1954) into a very effective cell killing agent. We have undertaken a phase I trial of Adenoviral-NTR, where patients who are going to undergo surgery to remove their liver cancer have a needle inserted into the cancer nodule, giving ultrasound guidance, through which the virus is injected. A few days later, the cancer tissue is removed and examined to see if the virus has infected the cancer cells and produced enough NTR to have an anticancer effect. So far the virus, which has been made by COBRA Therapeutics Ltd, Keele, is well tolerated, and we are seeing evidence of cancer cells expressing NTR. The next stage will be to combine the virus with CB1954 to see if we can demonstrate cancer shrinkage. Ultimately the virus can be delivered by injection through the hepatic artery or portal vein to increase the possibility of treating early stage liver cancer.

SECTION 5: GTAC POLICY FORUM – VIRAL VECTORS & GENE THERAPY

GTAC held a two-day forum in London in March 2002 to consider the benefits and risks of Lentiviral vectors and conditionally replicating viruses, as part of its "horizon-scanning" activity.

LENTIVIRAL VECTORS

The Lentiviruses are a family of viruses of which HIV is a member. Gene therapy vectors derived from lentiviruses raise specific safety, ethical and public health anxieties beyond those of more conventional gene delivery systems. However, Lentiviruses do not necessarily require cell division for infection and could therefore be used to achieve long-term expression in cells that would not be amenable to treatment using other gene therapy vectors.

The workshop identified basic principles that should underpin the consideration of the use of Lentiviral vectors by GTAC. The use of Lentiviruses raises issues for patient safety, public health and the public perception of gene therapy. Investigators will need to consider the implications of Lentivector studies to research staff, for example, in the case of needle-stick injury and sero-conversion. Given unknown risks are associated with Lentiviral administration, compelling reasons justifying the choice of vector, the patient group, including immune system status, and the approach (*ex vivo* versus *in vivo*) will be required. These will be over and above the requirements for protocols involving other gene therapy vectors. Investigators wishing to conduct Lentiviral trials are encouraged to contact the GTAC secretariat for discussions, prior to any formal protocol submission.

CONDITIONALLY REPLICATING VIRUSES

Conditionally Replicating Viruses (CRVs) are designed to be capable of selectively replicating in tumour cells, leading to their destruction, whilst sparing normal cells. The forum focussed mainly on Adenoviral vectors. Researchers are working to develop CRVs with tumour-selective promoters. To date, the use of CRVs, such as ONYX-015 or HSV1716, in patients has proven safe.

Although this field is maturing, it is still too early for GTAC to provide prescriptive advice to researchers proposing to use CRVs in cancer patients. Instead, researchers are encouraged to contact the GTAC secretariat for pre-proposal discussions prior to any formal submission. In the case of CRVs derived from Adenovirus, consultation of the report of the GTAC Adenovirus Working Party is strongly recommended.

Reference:

1. J. B. Connolly. Lentiviruses in gene therapy clinical research. Gene Therapy 2002; Volume 9; 1730–1734.

ANNEX A: GLOSSARY

AAV

Adeno-associated virus.

Adenovirus/adenoviral

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

APC (antigen presenting cell)

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

B-Cel

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.

Chemotherapy

Treatment with chemicals that destroy cancerous tissue.

Cell

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

CTL (cytotoxic T-lymphocyte)

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

CMV (cytomegalovirus)

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

Cytotoxicity

The property of being able to kill cells directly.

EBV (Epstein-Barr virus)

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

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.

Ganciclovir

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

Gene

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

Genetic disease or disorder

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

Germline cell

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

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.

HSV (Herpes simplex)

The virus responsible for causing cold-sores.

Immune response

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

Immunohistochemistry

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

Immunomodulation

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

In vitro

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

In vivo

When experiments are performed in living organisms.

Intraperitoneal

Within the cavity that contains the abdominal organs.

In Utero

In the womb (uterus).

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.

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.

Metastatic, metastases

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

MVA (Modified Vaccinia Ankara)

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

NGF (Nerve Growth Factor)

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

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.

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.

PIL

Patient Information Leaflet

Placebo

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

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. They are made inert so that they can enter a human cell carrying a gene for gene therapy without causing disease.

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.

Transduction

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

Tumour regression

A cancer that has become smaller or has completely disappeared.

Tumour suppressor gene

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

Unresectable

Unable to be fully removed by surgery.

Vaccinia

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

Vector

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

Virus

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

ANNEX B: GTAC ANNUAL REPORTS

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

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

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

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

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

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

[7] Seventh Annual Report January 2000-December 2000. Health Departments of the United Kingdom. London. Department of Health. 2002.

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

ANNEX C: TERMS OF REFERENCE

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

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

(2) To work with other agencies which have responsibilities in this field including local research ethics committees and agencies which have statutory responsibilities – the Medicines Control Agency, the Health and Safety Executive, and the Department of the Environment;

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

The Committee will have a responsibility for:

(a) Providing advice for applicants on:

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

  (ii) The design and conduct of the research;

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

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

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

  (i) The clinical status of the subjects;

  (ii) The scientific quality of the proposal;

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

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

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

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

ANNEX D: MEMBERSHIP OF GTAC

GTAC MEMBERS:

Professor Norman Nevin (Chairman)
Emeritus Professor of Medical Genetics, Queen's University, Belfast.

Ms Caroline Benjamin
Merseyside and Cheshire Clinical Genetics Service

Mrs Deborah Beirne
Research Sister, St. James Hospital, Leeds.

Mr David Crosby
Retired Surgeon, Cardiff

Professor Martin Gore
The Royal Marsden Hospital, London

Professor Terence Hamblin
University of Southampton and Royal Bournemouth Hospital

Dr Peter Harris
Technical Director, KuDOS Pharmaceuticals Ltd.

Professor David Harrison
Department of Pathology, Edinburgh University

Mr Michael Harrison
Lawyer, London

Professor Ian Hart
St Thomas' Hospital, London

Mrs Ann Hunt
Tuberous Sclerosis Association

Professor Nicholas Lemoine
Cancer Research UK Molecular Oncology Unit, Hammersmith Hospital, London

Professor Andrew Lever
Infectious Diseases, University of Cambridge

Professor Alex Markham
Molecular Medicine, University of Leeds

Professor James Neil
Virology, University of Glasgow

Rev. Dr Lee Rayfield
Vicar, Maidenhead, Berks

Ms Fiona Sandford
Patient Advocate, Hertfordshire

Dr. Michael Waterhouse
Media Producer and Author, Southborough

OBSERVERS

Department of Health:

Ms Elizabeth Woodeson

Medicines Control Agency:

Dr Elaine Godfrey

Dr Brian Davis

Dr Philip Harrison

Health & Safety Executive:

Dr Michael Mackett

SECRETARIAT

Dr John Connolly (Secretary)

Dr Jayne Spink

Mr Daniel Gooch

Mrs Margaret Straughan

ANNEX E: REGISTER OF MEMBERS INTERESTS

GTAC Member	Declared interests
Professor Norman Nevin	None
Professor Nick Lemoine	Research Unit supported by UK charities and commercial bodies. Director of Gene Expression Technologies Consultant on EntreMed, Gendux & IC-Vec
Ms Caroline Benjamin	Partner employed as financial accountant for, and has share options in, Evans Vaccines section of Powderject plc
Mr David Crosby	None
Professor Martin Gore	Ad hoc consultancy to Schering-Plough, Bristol-Myers Squibb, Aventis, Novartis, Pierre Fabre, Debiopharm, and Chiron. Consultant, Cambridge Antibody Technology
Professor Terence Hamblin	None
Mr Michael Harrison	None
Professor David Harrison	Shares – Medical Solutions & The Forensic Institute University consultancy – Fairfield Imaging, Scottish Medicine, Quintiles Directorship – EMMS (International) and EMMS (Nazareth) – both registered charities
Professor Ian Hart	None
Mrs Ann Hunt	None
Professor Andrew Lever	Consultancy & Shareholding in SynGenix Ltd
Professor Alex Markham	Scientific Advisory Board Member of Oxagen Ltd. Director of, & shareholding in, Molecular Solutions Ltd. Director: Bioscience Venture Capital Trust Director: Bioconsulting Ltd.
Professor James Neil	None
Mrs Deborah Beirne	Work involves gene therapy trials.
Dr Peter Harris	Consultant to ML Laboratories Plc
Reverend Lee Rayfield	None
Ms Fiona Sandford	Shares in Australian Mutual Provident
Dr Michael Waterhouse	None
Dr John Connolly	Spouse employed as Scientific Advisor on HIV by Bristol-Myers Squibb

ANNEX F: EXTERNAL EXPERT ADVISERS TO GTAC

GTAC is extremely grateful to the following people for their support in the review of applications and for their input of expertise and advice:

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

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

ANNEX G: MODIFICATIONS OF GTAC APPROVED STUDIES

During 2002 GTAC received a total of thirty-nine applications to amend ongoing studies. Thirty-six of these were approved following favourable review and three were declined:

JANUARY

GTAC036: Modification of patient exclusion criteria and study procedures. Alterations to study personnel and administrative structure.

GTAC029B: Addition of a centre and investigator (Southampton). Changes to the protocol text.

GTAC054: Minor amendments to the text of the patient information leaflet.

GTAC032: Minor modifications to protocol text and patient information, including changes to study personnel.

GTAC055: Modifications to protocol text, patient information and study personnel.

GTAC042: Approval of additional investigator and site (Christie Hospital, Manchester). Modification of protocol and patient information.

GTAC031: Minor modifications to protocol text and patient information, including study personnel.

FEBRUARY

GTAC047: Update of the investigator brochure and protocol.

GTAC052: Change of principal investigator.

GTAC060: Amendment to protocol and patient information.

GTAC045: Amendment to inclusion criteria.

GTAC062: Minor change to selection criteria. Changes to the patient information leaflet requested by LREC.

GTAC039: Conditional approval for change to method of administration of study product.

MARCH

GTAC064: Revision of patient information and clinical protocol as requested by GTAC.

GTAC055: Approval for dose escalation in accordance with adenoviral working party recommendations.

GTAC060: Minor amendments to protocol text and patient information.

GTAC045: Amendment to inclusion criteria.

MAY

GTAC029B: Change to monitoring schedule.

GTAC029A: Change to monitoring schedule, including additional monitoring.

JUNE

GTAC062: Amendment of dosage level.

GTAC062: Minor changes to the exclusion criteria.

GTAC060: Addition of new investigator.

GTAC039: Additional mode of delivery of cancer vaccine.

GTAC051: Minor changes including clarifications to the exclusion critera, extension of follow-up and changes to study personnel.

GTAC036: Modification of exclusion criteria, selection of study population and monitoring arrangements.

GTAC045: Request to treat a specific patient.

JULY

GTAC032: Approval for dose escalation in accordance with recommendations of adenoviral working party.

GTAC032: Application to amend inclusion criteria (declined).

AUGUST

GTAC054: Application for use of addition patient information (declined).

OCTOBER

GTAC062: Update of patient information.

GTAC032: Progression to inoperable arm of study.

GTAC062: Further update of patient information.

GTAC051: Introduction of new publicity arrangements (declined).

GTAC072: Additional Investigator and site (Western General Hospital).

GTAC018: Approval to re-treat two patients who showed evidence of a response to the treatment.

GTAC018B: Approval to re-treat one patient who showed evidence of a response to the treatment.

NOVEMBER

GTAC054: Changes to inclusion and exclusion criteria, additional tests and modifications to the patient information to reflect changes to the study protocol.

GTAC047: Update of the patient information.

GTAC057: Approval to retreat one patient who showed evidence of a response to the treatment.

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

LATEST U.K. GENE THERAPY RESEARCH 1993–2002 (FEBRUARY 2003)

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
001	Adenosine deaminase gene transfer in a child with severe combined immunodeficiency syndrome	SCID-ADA	Institute of Child Health/Great Ormond Street Hospital	1-93	Retrovirus	ADA	pOAM-P1	1 CLOSED
002	Gene Therapy Research for Cystic Fibrosis	CF Nasal trial	Royal Brompton Hospital	3-93	Plasmid	CFTR	*E coli* DM5_	15 CLOSED
003	A pilot study of idiotypic vaccination for follicular B-cell lymphoma using a genetic approach	B-cell lymphoma	MRC Cambridge	7-93	Plasmid	anti-idiotype immunoglobulin	–	7 CLOSED
004	Use of gene transfer to determine the role of tumour cells in bone marrow used for autologous transplantation and the efficiency of immunomagnetic "purging" the bone marrow	Neuroblastoma	ICRF Bristol	2-94	Retrovirus	LNL-6/neo G1N-neo	PA317	Trial withdrawn
005	Gene Therapy for metastatic melanoma: Assessment of expression of DNA constructs directly injected into metastases	Metastatic melanoma	ICRF Oxford	5-94	Plasmid	IL-2	*E coli* JM109	23 CLOSED
006	The treatment of metastatic malignant melanoma with autologous melanoma cells that have been genetically engineered to secret IL-2	Metastatic melanoma	Institute of Cancer Research/Royal Marsden Hospital	2-94	Retrovirus	IL-	GP+env AM12	12 CLOSED
007	Towards gene therapy for cystic fibrosis	CF Nasal trial	Oxford/Cambridge	2-94	Plasmid	CFTR	*E coli*	18 CLOSED
008	Gene Therapy Research for Cystic Fibrosis	CF Nasal trial	Edinburgh	5-94	Plasmid	CFTR	*E coli*	16 CLOSED
009	Gene Therapy Research for Cystic Fibrosis	CF Lung trial	Royal Brompton Hospital	9-94	Plasmid	CFTR	*E coli*	CLOSED

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
010	Transfer of the Human Multi-drug Resistance Gene into the Haemopoietic Cells of Patients Undergoing High Dose Therapy and Autologous Stem Cell Transplantation for Malignant Lymphoma	Lymphoma	University College London Medical School	12-94	Retrovirus	MDR-1	AM12M1	3 CLOSED
011	Genetic prodrug activation therapy for breast cancer	Breast Cancer	Hammersmith Hospital	10-95	Plasmid	Cytosine deaminase	*E coli*	12 CLOSED
012	Use of a recombinant vaccinia virus for therapy of cervical cancer	Cervical Carcinoma	University of Wales, Cardiff	6-95	Vaccinia	TA-HPV	MRC5	1+8 CLOSED
012A	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat Cervical intraepithelial neoplasia III	Cervical intraepithelial neoplasia III	University of Wales, Cardiff	5-96	Vaccinia	HPV E6 and E7	MRC5	12 CLOSED
012B	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat Cervical intraepithelial neoplasia III	Cervical intraepithelial neoplasia III	University of Wales, Cardiff/University of Manchester	8-97	Vaccinia	HPV E6 and E7	MRC5	8 CLOSED
012C	Use of recombinant Vaccinia vaccine (TA-HPV) to treat Vulval intraepithelial neoplasia III	Vulval Intraepithelial Neoplasia III	St Mary's Hospital, Manchester	1-00	Vaccinia	HPV E6 and E7	MRC5	18 CLOSED
012D	Use of a recombinant Vaccinia vaccine (TA-HPV) to treat Ano-genital intraepithelial neoplasia III	Ano-genital intraepithelial neoplasia III	Addenbrooke's Hospital, Cambridge	4-00	Vaccinia	HPV E6 and E7	MRC5	12 CLOSED
013	A proposal to study the efficacy of transplantation of autologous retroviral transduced bone marrow in patients homozygous for the W402X mutation (Hurlers syndrome)	Hurlers Syndrome	Royal Manchester Children's Hospital, Manchester	12-95	Retrovirus	pLX	GP+env AM12	3 CLOSED

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
014	Phase I, Open-Label, Dose-Escalation Trial of Intra-Tumoral Injection with an E1B Attenuated Adenovirus ONYX-015, into Recurrent and Locally Advanced p53(-) Squamous Cell Tumours of the Head and Neck	Head and Neck Cancer	Beatson Oncology Centre, Glasgow	1-96	Adenovirus	E1B deleted	HEK293	22 CLOSED
014A	A phase II trial of intravenous cisplatin, 5-FU and intratumoral injection with ONYX-015 into recurrent, chemotherapy naive squamous cell tumours of the head and neck	Head and Neck Cancer Phase II Study	Beatson Oncology Centre, Glasgow	7-97	Adenovirus	E1B deleted	HEK293	37 CLOSED
014B	Phase I, Open-Label, Dose-Escalation Trial of Intraperitoneal Injection with an E1B Attenuated Adenovirus in patients with recurrent/refractory ovarian carcinomas	Recurrent/ refractory ovarian cancer	Beatson Oncology Centre, Glasgow	2-97	Adenovirus	E1B deleted	HEK293	12 CLOSED
015	Towards gene therapy for Cystic Fibrosis	CF Nasal Trial	Oxford/Cambridge/ Leeds/Manchester Consortium	5-96	Plasmid	CFTR	*E coli*	11 CLOSED
016	Phase I study in patients with recurrent metastatic squamous cell carcinoma of the head and neck using SCH 58500 (rAd/p53)	Head and Neck Cancer	Institute of Cancer Research/Royal Marsden Hospital	9-96	Adenovirus	p53	HEK293	Trial did not open
017	Gene therapy for Cystic Fibrosis Delivery to nasal epithelium and lung by nebulisation of the pCFICFTR/#67	CF Lung and Nasal Trial	Royal Brompton Hospital	11-96	Plasmic	CFTR # 67	*E coli* TGI	16 CLOSED
018	A Phase I dose-escalation study of intratumoral injection with modified HSV Type I (ICP 34.5-) into primary and recurrent malignant glioma	Glioblastoma	Beatson Oncology Centre, Glasgow	12-96	HSV	ICP34.5 deleted	BHK 21/C13	9 CLOSED

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
018A	A Phase I dose-escalation study of intratumoral injection with modified HSV Type I (ICP 34.5-) into primary and recurrent malignant glioma	Glioblastoma	Beatson Oncology Centre, Glasgow/ Institute of Neurological Sciences, Glasgow/ Queen Elizabeth Hospital, Birmingham	7-99	HSV	ICP34.5 deleted	BHK 21/C13	12 CLOSED
018B	A study of the safety of the modified Herpes simplex virus (HSV 1716) when injected into tumour bearing brain following resection of recurrent or newly diagnosed high grade glioma	Glioblastoma	Beatson Oncology Centre, Glasgow	11-00	HSV	ICP34.5 deleted	BHK 21/C13	8 CLOSED
019	GTI 0115 radiation and infection of murine cells producing HSV TK vector followed by intravenous ganciclovir against the efficacy of surgery and radiation in the treatment of newly diagnosed previously untreated glioblastoma (tumour site)	Glioblastoma	Beatson Oncology Centre, Glasgow/ Institute of Neurological Sciences, Glasgow	9-96	Retrovirus	TK	PA317	Trial withdrawn
020	A clinical trial with Ad-5CMV-p53 vector in patients with ascites formation	Gastrointestinal cancer/ malignant cancer ascites	Royal Marsden Hospital, London	4-97	Adenovirus	P53	Hek293	1 CLOSED
021	Phase II study of immunotherapy of advanced breast cancer by repeated intramuscular injection of recombinant vaccinia viruses containing sequences coding for human MUC-1 and IL2 (TG1031)	Breast Cancer	Guy's Hospital, London	11-97	Vaccinia	MUC-1 IL2	–	14 CLOSED

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

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
027	The use of MetXia-P450 for the treatment of advanced breast cancer (Phase I/II intratumoral)	Breast Cancer	The Churchill, Oxford	10-98	Retrovirus	Cytochrome P450	TEFLY-A	12 CLOSED
028	A phase I/II study of hepatic artery infusion with WTP53-CMV-AD in primary metastatic malignant liver tumours	Liver Cancer	Hammersmith Hospital, London	Application Withdrawn	Adenovirus	p53	HEK293	Application withdrawn
029A	A Phase I/II pilot study of idiotypic vaccination for follicular B-cell lymphoma using a genetic approach (i.m.)	B-cell lymphoma	Royal Bournemouth Hospital and Royal South Hampshire Hospital, Southampton	5-99	Plasmid	Idiotypic DNA vaccination	*E coli* JM109	17
029B	A pilot study of donor idiotypic vaccination for the purpose of targeted post-transplant immunotherpay following allogenic bone marrow transplantation for multiple myeloma	Multiple Myeloma	Royal Bournemouth Hospital and Royal South Hampshire Hospital, Southampton	5-00	Plasmid	Idiotypic DNA vaccination	*E coli* JM109	4
029C	Phasel/II study of Idotypic vaccination for multiple myeloma usinf a genetic approach (MMIFTT)	Multiple Myeloma	Royal Bournemouth Hospital and Royal South Hampshire Hospital, Southampton	4-00	Plasmid	Idiotypic DNA vaccination	*E coli* JM109	Trial not yet open
029D	Phase I/II study of idiotypic vaccination for chronic lymphocytic leukaemia uisng a genetic approach (CLLIFTT)	Chronic Lymphocytic Leukaemia	Royal Bournemouth Hospital and Royal South Hampshire Hospital, Southampton	4-00	Plasmid	Idiotypic DNA vaccination	*E coli* JM109	1
030	Use of a retrovirus carrying human cytochrome p450 for the treatment of ovarian cancer (Phase I intra-abdominal)	Ovarian Cancer	Northern General Hospital, Sheffield	2-00	Retrovirus	Cytochrome P450	TEFLY-A	6 CLOSED

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
031	Gene directed enzyme prodrug therapy for the treatment of head and neck cancer (Phase I intratumoral)	Head and Neck Cancer	CRC Institute for Cancer Studies, University of Birmingham	7-99	Adenovirus	Nitroreductase	PER-C6	1
032	Gene directed enzyme prodrug therapy for the treatment of liver cancer (Phase I intratumoral)	Liver Cancer	CRC Institute for Cancer Studies, University of Birmingham	7-99	Adenovirus	Nitroreductase	Per-c6	12
033	Phase I trial of immunotherapy with adenovirus-interferon-g in malignant melanoma (intratumoral)	Malignant Melanoma	St. George's Hospital	7-99	Adenovirus	IFN-g	–	1 CLOSED
034	A phase II/III trial of chemotherapy alone versus chemotherapy plus Adp53 in ovarian and primary intraperitoneal cancer (intraperitoneal)	Ovarian Cancer	Royal Marsden Hospital/ Christie Hospital/ CRC Institute for Cancer Studies/ John Radcliffe Hospital	7-99	Adenovirus	p53	HEK293	1 CLOSED
035	Phase II trial of pre-operative intratumoral injection with an E1B attenuated adenovirus in patients with resectable head and neck tumours	Head and Neck Cancer	Beatson Oncology Centre, Glasgow	7-99	Adenovirus	E1B deleted	HEK293	15 CLOSED
036	The safety and effects of Ad5.1 mediated human FGF-4 gene transfer in patients with peripheral arterial occlusive disease (PAOD) Fontaine stage III (Phase I i.m.)	Peripheral Arterial Occlusive Disease	St George's Hospital, London	10-00	Adenovirus	FGF-4	PER-C6	–
037	A Phase III study of quadruple HAART follwed by double-blind randomisation to HIV vaccination wwith ALVAC-HIV and Remune or placebo	HIV	Chelsea & Westminster Hospital, Royal Free Hospital, Brighton General Hospital, University Hospital of Wales, Cardiff	5-00	Canarypox	HIV-1 env, gag	AVIAN	10

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
038	A Phase I, open label, dose escalation trial to assess the safety and immunogenicity of DISC-GMCSF in patients with mestatatic melanoma	Malignant melanona	Churchill Hospital, Oxford Royal Marsden Hospital, London	5-00	HSV	hGMCSF	CR2C9 (Vero-derived)	10
039	Gene therapy protocol for the evaluation of the safety, biodistribution and efficacy of Trovax in patients with metastatic colorectal cancer (Phase I i.m.)	Colorectal cancer	Christie Hospital NHS Trust, Manchester	10-00	Vaccinia	Human oncofoetal antigen 5T4	CEF	14
040	A Phase I dose escalation trial of an E1B attenuated adenovirus as an intravesical therapy for recurrent superficial/muscle invasive bladder cancer	Bladder cancer	St James's University Hospital, Leeds	Conditional Approval 7-00	Adenovirus	E1B deleted	HEK293	–
041	Randomised multi-centre trial evaluating two different vaccination schedules of MVA-MUC-1-IL-2 in women with metastatic breast cancer (Phase II i.m.)	Breast cancer	Guy's Hospital, London	Application withdrawn	Vaccinia	MUC-1, IL-2	CEF	–
042	Phase I study of melanoma poly-epitope DNA and melanoma poly-epitope modified vaccinia Ankara in patients with melanoma	Melanoma	The Churchill Hospital, Oxford	7-00	Vaccinia DNA	Mel3 (melanoma antigens)	CEF	14
043	A phase I/II trial of polyHER2neu-a polyepitope DNA vaccine encoding HER-2 epitopes in the treatment of epithelial cancers (i.m.)	Breast cancer	St James's University Hospital, Leeds	Application Declined	Plasmid	HER-2 epitopes	–	–

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
044	Treatment of leukaemic relapse after allogeneic stem cell transplantation by HSV-tk transduced donor lymphocyte transfusions	Chronic myeloid leukaemia	Hammersmith Hospital, London	10-00	Retrovirus	HSV -tk	AM12	10
045	Phase I clinical gene therapy protocol for X-SCID	X-SCID	Institute of Child Health, London	01-01	Retrovirus	Common gamma chain	PG13	4
046	Phase I gene therapy protocol for X-CGD	X-CGD	Institute of Child Health, London	12-00	Retrovirus	Gp91-phox	HEK293	1
047	A phase I, Randomised, Double-blind, Placebo Controlled, Escalating Dose, Multicentre Study of Ad2/Hypoxia Inducible Factor Gene Transfer Administered by Intramyocardial Injection During Coronary Artery Bypass Grafting Surgery in Patients with Incomplete Revascularisation	Coronary artery disease	John Radcliffe Hospital, Oxford	12-00	Adenovirus	HIF-1a/VP16	HEK293	Trial not yet open in the UK
048	A randomised phase I trial of intravenous CI-1042 with or without entanercept in patients with metastatic carcinoma	Metastatic carcinoma	Hammersmith Hospital, London	12-00	Adenovirus	p53	HEK293	– Application withdrawn
049	A phase I/II Study of Immunotherapy for Patients with Metastatic Melanoma Using Dendritic Cells Transfected with a Plasmid Encoding Two Melanoma Antigens	Metastatic Melanoma	CRC Institute for Cancer Studies, Birmingham	02-01	Plasmid complexed with peptide	MART-1 gp-100	*E coli*	–
050	A Phase II Trial of Preoperative Intratumoural Injection with HSV1716 in Patients with Resectable Squamous Cell Tumours of the Head and Neck	Head and Neck Cancer	Southern General Hospital, Glasgow	05-01	HSV	ICP34.5 deleted	BHK-21/C13	–

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
051	A European and Canadian Multicentre, randomised, double-blind, placebo controlled study to evaluate the efficacy and safety of Ad5FGF-4 in patients with Stable Angina	Coronary Artery Disease	Papworth Hospital, Cambridge	05-01	Adenovirus	FGF-4	HEK293	–
052	A phase I study to evaluate the safety, tolerability and immunogenicity of two administrations of either plasmid DNA (pSG.HBs) versus placebo or modified vaccinia virus Ankara (MVA.HBs) versus placebo, followed by two boost administrations of MVA.HBs expressing hepatitis B surface antigen in healthy male volunteers	Hepatitis B Vaccine Trial	TNO BIBRA International, Surrey	08-01	Vaccinia & plasmid	HBsAg	MVA: Chicken embryo fibroblasts Plasimd: I DH5_	–
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	AIDS	John Radcliffe Hospital, Oxford	05-01	Plasmid	HIV-1 clade A gag and 25 HIV-1 gag/pol/env/ nef CTL epitopes	I DH1	–
054	A Phase II, Randomised, Double-Blind, Placebo-controlled, Parallel Group, Efficacy and Safety Study of NV1FGF in Patients with Severe Peripheral Artery Occlusive Disease	Peripheral Artery Occlusive Disease	St. George's Hospital, London	08-01	Plasmid	FGF-1	I XAC-1	–
055	Gene directed enzyme prodrug therapy for the treatment of prostate cancer (Phase I intratumoral)	Prostate Cancer	CRC Institute for Cancer Studies, University of Birmingham	04-01	Adenovirus	Nitro reductase	PER-C6	–

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
056	A Phase II, Multicentre, Double-Blind, Placebo-Controlled, Dose-Finding Study of ZYC101a in the Treatment of High-Grade Squamous Intra-Epithelial Lesions of the Uterine Cervix	AnoGenital Neoplasia III	Hammersmith Hospital, London	11-01	Plasmid	HPV E6 & E7	*E coli*	– Not yet open
057	A Phase I, Multidose Study to Evaluate the Safety of Intramuscular Injections of HER-2 DNA in Patients with Metastatic Breast Cancer	Breast Cancer	Hammersmith Hospital, London	11-01	Plasmid	HER-2	*E coli*	9
058	The Use of a cDNA Vaccine Encoding the Human MUC1 Gene in the Treatment of Patients with Advanced Breast Cancer – A Phase I/II Study	Breast Cancer	ICRF, Guy's Hospital, London	08-01	Plasmid	MUC-1	*E coli*	–
059	TA-HPV recombinant vaccinia virus expressing the human papillomavirus 16 and 18 E6 and E7 proteins: Application to amend currently approved protocol to add a clinical trial involving a prime-boost strategy of TA-CIN administered in association with TA-HPV in high grade ano-genital intraepithelial neoplasia (AGIN) patients (PB-HPV/01)	Cervical Cancer	University of Wales, Cardiff, St. Mary's Manchester; Addenbrooke's, Cambridge	07-01	Vaccinia	E6 & E7 HPV	MR-5	10
060	Study of Transfection Efficacy and Safety of MetXia-OB83 in patients with cutaneous lesions of breast cancer or melanoma	Breast Cancer	The Churchill Hospital, Oxford	07-01	Retrovirus	P450	TEFLYRD	–
061	An upward titration study of transfection efficacy and safety of Metxia-OB83 in patients with adenocarcinoma of the prostate	Prostate Cancer	The Christie Hospital, Manchester	08-01	Retrovirus	P450	TEFLYRD	–

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
062	First Administration to Man of an Oncolytic Herpesvirus Vector Containing a Transgene for Granulocyte Macrophage Colony Stimulating Factor (OncoVex^{GM-CSF}) – A Study of its Safety, Biodistrubution and Biological Activity	Melanoma, Breast, Nead & Neck, cancer, Non-Hodgkins Lymphoma	Hammersmith Hospital, London	11-01	HSV	ICP34.5-deleted ICP47-deleted Human GM-CSF	BHK 21c13	–
063	VTP-1/01: A Phase I/II Trial of Intravenous vs. Hepatic Arterial Infusion of an E1A-CR2 Deleted Adenovirus (VTP-1) in Patients with Inoperable, Metastatic Colorectal Carcinoma	Metastatic Colorectal Carcinoma	Hammersmith Hospital, London	Application Withdrawn	Adenovirus	EiA conserved region 2 deleted & E3B RID gene region deleted	HEK-293	– Application withdrawn
064	A Phase I trial of replication-competent herpes simplex virus (ICP 34.5 null mutant 1716) in patients with inoperable malignant pleural mesothelioma	Mesothelioma	University of Glasgow	25 February 2002	HSV HSV1716	-ICP{34.5 deleted	BHK	–
065	A Phase I trial of PolyMEL, a polyepitpe DNA vaccine in the treatment of metastatic melanoma patients	Melanoma	St James Hospital, Leeds	2 January 2002	Plasmid DNA	Multiple Melanoma epitopes	*E coli*	–
066	A recombinant vaccinia Ankara (MVA)-based vaccine encoding Epstein-Barr Virus target antigens: A trial in helathy volunteers	Naso-Pharyngeal carcinoma	Institute of Cancer Studies, Birmingham	25 February 2002	DNA plus MVA	EBV epitopes	CEF	–
067	Percutaneous Intramyocardial Gene Therapy against myocardial ischemia with phVEGF-A165SR – A double-blind placebo controlled study	Coranory Artery Disease	Wythenshawe Hospital, Manchester	Application Pending	Plasmid	VEGF	*E coli*	– Application pending

GTAC No.	Protocol Name	Details	Centre	Outline Approval	Vector	Gene	Cell line	No. of patients
068	A Phase I trial of polyHER2neu – a polyepitope DNA vaccince encoding HER-2 epitopes in the treatment of breast cancer	Breast Cancer	St James Hospital, Leeds.	2 January 2002	Plasmid	Poly epitopes of Her-2	*E coli*	–
069	A phase I/II study of DNA vaccination against a CMV/FrC of tetanus toxin fusion gene in allograft donors and recipients	Cytomegalovirus infection following transplant	Southampton University Hospitals	12 June 2002	Plasmid	pp65 from CMV	*E coli*	Application under review
070	Number not allocated							
071	A Phase I/II prospective study of immunogene therapy with a liposomally encapsulated replication incompetent Semliki Forest Virus (SFV) vector carrying the human interleukin-12 gene and administered intratumorally in patients with recurrent or progressing glioblastoma multiforme	Glioma	University of Liverpool	Application Under Review	Replication disabled Semliki Forest Virus	IL-2	–	–
072	Phase I/II study to determine the optimum dose and dosing regimen then to assess the efficacy of a poly-epitope pharmaccine (therapeutic vaccine), involving pSG2.Mel3 and MVA.Mel3, in patients with Stage III or Stage IV metastatic melanoma	Melanoma	University of Manchester	09-02	DNA and MVA	Multiple Melanoma epitopes	CEF	–
073	Phase I clinical gene therapy protocol for adenosine deaminase deficiency	Severe Combined Immuno-deficiency	Great Ormond Street Hospital, London	Application Under Review	Retrovirus	Adenosine Deaminase	PG13	–

The GTAC Secretariat may be contacted at:

Department of Health
652c, Skipton House
80 London Road
Elephant & Castle
London SE1 6LH

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