Annual report : 2008 / Gene Therapy Advisory Committee.

GTAC

GENE THERAPY ADVISORY COMMITTEE

FIFTEENTH ANNUAL REPORT

Covering the period from January 2008 to December 2008

Health Departments of the United Kingdom

2009

About the Gene Therapy Advisory Committee (GTAC)

The Gene Therapy Advisory Committee (GTAC) is a Non-Departmental Public Body (NDBP), acts independently of Ministers and is recognised as a Research Ethics Committee by the UK Ethics Committee Authority (UKECA). Under the the Medicines for Human Use (Clinical Trials) Regulations 2004, GTAC has UK-wide statutory responsibility for the ethical oversight of clinical trials involving gene therapy. GTAC's terms of reference also include the ethical oversight of clinical trials involving cell therapies derived from stem cell lines. The Committee advises Ministers on the development and use of gene and stem cell therapies and works with other Government agencies with an interest in this area, such as the Medicines and Healthcare products Regulatory Agency (MHRA), the Health and Safety Executive (HSE) and the Human Tissue Authority (HTA). GTAC's Secretariat is provided by the Department of Health for England.

The GTAC Secretariat may be contacted at:

Department of Health

Area 604, Wellington House

133-155 Waterloo Road

LONDON SE1 8UG

Tel: 020 7972 3057

Fax: 020 7972 4300

Email: gtac@dh.gsi.gov.uk

Website: http://www.dh.gov.uk/ab/GTAC/index.htm

GTAC

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FOREWORD

Welcome to the Fifteenth Annual Report of the Gene Therapy Advisory Committee (GTAC) which covers the Committee's work from January 2008 to December 2008.

GTAC has now been in existence for 15 years and over that period the concept of 'Gene Therapy' has evolved considerably. Gene therapy applications have, without doubt, become increasingly elaborate and ambitious. Indeed, when the Committee was first established in 1993, gene therapy was a very new and raw science, primarily targeting conditions caused by defects to single genes in patient's genomes. In the intervening years, a dedicated cohort of researchers have gained considerable understanding of a vast array of these single gene disorders and have energetically pursued novel ways of attempting to treat those conditions. Perhaps even more edifyingly, we have also seen a proliferation of innovative and exciting applications of gene therapy that aim to tackle some of the most common and complex conditions like coronary disease, neurological disorders and many of the cancers. This broadening of gene therapy as a potential treatment platform is reflected in the steady stream of high quality and diverse applications that come before the Committee.

Over those same 15 years of GTAC, another therapeutic area has emerged and, indeed, in some cases, converged with gene therapy; that of stem cell research. Reflecting this development, the year 2008 saw United Kingdom Health Ministers extend GTAC's Terms of Reference to include the ethical oversight of clinical trials involving therapies derived using stem cell lines. This is the culmination of the Government's commitment to establish specialist ethic review for these kind of therapies, as recommended in the 'Pattison Report' on UK stem cell research in 2005. This 'new string to GTAC's bow' has been both challenging and exhilarating. Clinical research using stem cell lines raises a host of ethical issues. Some of these are very familiar to GTAC, but many of these issues are entirely novel, not just to GTAC, but the entire field of medicine. Ensuring the best possible stem cell clinical research can take place in the UK will no doubt keep the committee exercised for many years to come.

That being said, the core business of GTAC still remains ethical oversight of gene therapy clinical trials. Over the previous years, GTAC has helped shape high quality gene therapy research to patients. By now, the Committee has progressed many trials from the first in man stage all the way through to the phase III studies involving many hundreds of patients. Recognising a field that is growing in maturity, the Clinical Trials Regulations were amended in 2008 to allow GTAC to transfer gene therapy studies to other Research Ethics Committees (RECs) where they have been deemed to be of "low genetic risk." This approach is part of a long-standing commitment by GTAC to de-mystify gene therapy and encourage its safe and ethical integration into mainstream biomedical research. During 2008 two applications received by GTAC fell into this category and were, happily, very smoothly transferred from GTAC to non-specialist RECs for review.

Those transferred applications were part of a tally of 18 applications to the Committee over 2008, producing another busy and productive year. A key aspect in oversight of applications comes from the role played by our external reviewers. I wish to warmly thank those expert external reviewers, both in the UK and overseas, who have so generously contributed their time and expertise. Their commitment helps to ensure

that gene therapy in the UK continues to be conducted to the highest standards. Likewise, I warmly extend my thanks to each one of the members of GTAC. It is one of the greatest strengths of GTAC that its members consistently show enormous dedication and commitment to the Committee and its vital role in gene therapy research.

But above all, I must pay tribute the patients who volunteer to take part in those gene therapy trials that GTAC approves. The highest percentage of those studies involves cancers in their advanced stage, where other treatment options have been exhausted. I always feel very humbled and grateful that patients who have had to come to terms with their condition are yet still willing to be invvoled in a further experimental study, with no guarantee of success nor expectation of personal benefit. Advances in medical knowledge and treatments is entirely due to the involvement of these generous and selfless people, who are most certainly entitled to be considered by us all as fellow collaborators rather than participants.

I hope you will find this report of interest.

Professor Martin Gore

Chairman of GTAC

SUMMARY

In 2008, GTAC considered sixteen new applications to conduct gene therapy clinical trials in the UK under its remit as the National Research Ethics Committee for gene and stem cell therapy clinical research. As with previous years, the majority of applications (six, 38%) focussed on various cancers. Applications for infectious diseases were the next highest group (four, 25%), closely followed by single gene disorders (three, 19%). More detailed information on all applications is contained in Section 1.

In its lifetime, the Committee has reviewed 170 applications. Of these, 145 trials have come to fruition, with 89 closed to patient enrolment and 56 currently open or due to open for recruitment. The remaining 25 applications were either declined by the Committee or never recruited patients as they were withdrawn following initial GTAC approval. Short summaries on some of the studies which have closed during 2008 are given in Section 4.

Over the years GTAC has continued to ensure delivery of high quality gene therapy research to patients. The Committee has seen and encouraged successful trials progress from the first in man stage through to the phase III stage where hundreds of patients may be treated in order to prove the safety and efficacy of the treatment. In May 2008 an Amendment to the Clinical Trials Regulations permitted GTAC to transfer studies deemed 'low risk' to three other nominated UK Research Ethics Committees. This approach is part of a long-standing commitment by GTAC to de-mystify gene therapy and encourage its safe and ethical integration into mainstream biomedical research. During 2008 two studies fell into this category and were transferred out. Further information is available in Section 1.

The Amendment to the Clinical Trials Regulations has also seen a change to GTAC's Terms of Reference which extended GTAC's remit to review applications for clinical trials involving stem cell lines. The Committee is also regularly kept informed of current development in stem cell initiatives in order to fulfil its obligations as an Advisory Body as well as having the appropriate knowledge and expertise when the first application for a clinical trial using stem cell lines is presented.

Also in line with all the above activities 2008 was a timely point at which to review the GTAC Standard Operating Procedures and to also produce Supplementary Operating Procedures for those applications which would meet the criteria for being transferred. These documents are available to view on the GTAC website at:
http://www.dh.gov.uk/ab/GTAC/AboutGTAC/index.htm

This year has also seen the adoption of a new GTAC application form based in an online system called IRAS (Integrated Research Application System). This has come about as a collaborative initiative which is supported by many organisations in an integrated effort to reduce bureaucracy for researchers and to streamline their path to commencing research. We completely support this initiative as the regulatory path for researchers can be seen as difficult and obstructive.

The final section of this report details GTAC's terms of reference, membership and external expert advisers who have given of their time so generously in providing expert comments on new applications. Between 1993 and 2008, GTAC has recorded the participation of approximately 1,800 patients in UK gene therapy trials.

SECTION 1: PROTOCOLS REVIEWED BY GTAC IN 2008

In 2008, GTAC reviewed 16 new applications (GTAC 146 to 159). Included in this number was a resubmitted application that had been reviewed some years ago and whose design and methodology had been considerably improved (GTAC 115) and a follow up sub-study to an ongoing trial (GTAC 99A). Two further applications were transferred out as they met the criteria to be considered 'low risk' gene therapy.

1.1 Cancer

Cancer is a multi-factorial disease where cells escape the body's control mechanisms and invade, erode and destroy normal tissue. The driving forces in the development of cancer are the cell's genes which can become damaged by a variety of factors such as the environment, diet and life-style. The chance of developing cancer can also be increased by an individual's genetic make-up, for example, in the case of familial breast and ovarian cancer, due to mutations in the BRCA and other genes. There are over 200 different types of cancer that can occur anywhere in the body. Surgery is usually the treatment of choice, however, cancer is less amenable to curative surgery once it has spread beyond the original tumour (metastasised). Gene therapy offers a new, but still experimental, potential treatment that could complement conventional treatments such as surgery, chemotherapy and radiotherapy. In fact, over 60% of all gene therapy clinical trials in the UK aim to develop treatment for cancer.

1.1.1 Leukaemia (Blood Cancer)

Acute Lymphoblastic Leukaemia or ALL is cancer of the bone marrow or cancer of the white blood cells. ALL is one of the four main types of leukaemia. It is mostly seen in children where there are about 400 cases per 100,000 in the UK with the average age between the ages of 1-4. Around a third of all cancers seen in children are leukaemia with three quarters of them being ALL.

ALL relates to the overproduction of immature lymphocytes called lymphoblasts – or 'blast cells'. In individuals with ALL, production of the blast cells goes into overdrive, this means that these cells do not mature. These immature cells 'fill up' the bone marrow cavity which in turn stops other cells being made properly. There are two different types of blast cells T-lymphocytes and B-lymphocytes, each creating different cells: T-lymphocytes create various types of blood cell and B-lymphocytes make antibodies which attack infecting bacteria, viruses etc.

The cause of ALL is unknown. In the past there has been speculation that it could be linked to exposure to electromagnetic fields, high voltage electricity cables and household radon. All of these have been discredited recently. It is currently thought that ALL is due to a series of genetic changes to a particular group of immature blood cells. Though the causes remain not fully understood, it is thought that it could be triggered by an unusual reaction to a common infection.

Treatment for ALL is much the same as other leukaemias and is predominantly based on chemotherapy. About 80% of those diagnosed will get rid of the leukaemia – remission. Should relapse occur (the cancer returns) it is generally seen within a few years post remission. Patients are given further chemotherapy treatments or high dose chemotherapy or radiotherapy to the whole body (Total Body Irradiation) which removes all of the patient's bone marrow in preparation for a bone marrow transplant. The latter treatment can give a further remission in about 33% of people.

GTAC 147: Immunotherapy with CD19ζ chimeric antigenreceptor gene modified EBV specific CTLs after stem cell transplant in children with high-risk acute lymphoblastic leukaemia

This study proposes that a retroviral vector is used to modify a subtype of T cells from a healthy donor, namely EBV-specific CTLs (Epson Barr Virus specific Cytotoxic T lymphocyte cells). Transduction of donor T cells in the laboratory with the retroviruses modifies the cells to produce a receptor to target a cell surface protein called CD19 (anti-CD19). This means that the transduced donor CTLs can recognise and specifically destroy cells that have CD19 on their surface. Because CD19 is present almost exclusively on B cells (i.e. the leukaemic cells in the ALL patient) but absent on other (healthy) cells, the administration of transduced donor CTLs is hoped will clear ALL B-blasts in the patient.

This application was discussed at the February meeting and received approval.

1.1.2 Colorectal Cancer

Colorectal or bowel cancer is cancer of the colon or rectum. It is the third most common form of cancer and the second leading cause of cancer related deaths in the west, causing some 655,000 deaths per year worldwide. The cancer is usually asymptomatic until it has reached an advanced stage. This is why some organisations advocate regular screening for those in the high-risk category, as in the same way with all cancers the earlier it is caught the greater the chance of cure.

Colorectal cancer begins as adenomas (a group of growths) that resemble a polyp. Colon polyps are fleshy growths that occur on the inside (the lining) of the large intestine, also known as the colon. Colon polyps develop when chromosome damage occurs in cells of the inner lining of the colon. When certain types of polyps grow large enough, they can become cancerous. Therefore, removing benign colon polyps can prevent colorectal cancer. Initially, however, most polyps are benign and experts believe it takes around 5 years for these growths to become malignant. Treatment is very much dependent on when the cancer is found; it generally involves surgery followed by chemotherapy and occasionally radiotherapy (either before or after the surgery).

Metastatic Colorectal cancer describes a particular cancer that has spread, or metastasized, through either the bloodstream or the lymph node system to other parts of the body for instance the liver or lungs.

GTAC 149: A multicentre, double blind, placebo controlled, randomized study of TroVax vs placebo in the first line treatment of patients with metastatic colorectal cancer receiving standard of care

The product TroVax is well known to GTAC. TroVax is based on highly attenuated Modified Vaccinia Ankara (MVA) virus and contains the gene for a human glycoprotein called oncofetal antigen (or 5T4). 5T4 is found on the surface of many cancer cells. As with most cancer gene therapy approaches, the strategy here is "immunotherapy": it is to inform the immune system to the presence of the cancer cells (i.e. those that have 5T4 on their surface) so that the immune system of the patient can target and kill the cancer cell.

This application was discussed at the February meeting and received approval.

1.1.3 Pancreatic Cancer

Pancreatic cancer is not that common a cancer in the UK with between 7000-7500 patients diagnosed per year. The pancreas is part of the digestive system producing both digestive enzymes that help break down the food in the small intestine (such as fat); the other 'job' of the pancreas is to produce insulin. Insulin regulates blood sugar levels; the higher the blood sugar level the more insulin is released into the blood stream.

There are different types of pancreatic cancer but they can be classified into two main types depending on where the cancer is. If it is inhibiting the production of digestive juices it is called exocrine pancreatic cancer and if it inhibits the production of insulin and other hormones then it is known as endocrine pancreatic cancer.

Overall survival for those with pancreatic cancer is not good which is largely due to the cancer generally being quite advanced when initially diagnosed. The vast majority of people will not reach 5 year survival. Often it also means that surgery to remove the cancer is not possible as it has already spread. Currently there are trials underway to give patients radiotherapy or chemotherapy before surgery to help shrink the tumour before an operation. As surgery for this type of cancer is a major operation the treatment according to NICE guidelines is the chemotherapy drug Gemcitabine.

GTAC 152: A phase 1-2 multicentre, open-label study of the X-linked inhibitor of apoptosis (XIAP) antisense AEG35156 given in combination with Gemcitabine in patients with advanced pancreatic cancer

The study proposes to administer AEG35156, a chemically synthesized second generation antisense to human XIAP mRNA. XIAP (X-linked inhibitor of apoptosis (Cell death)) is the most potent IAP and is commonly present at elevated concentrations in cancer cells. The approach taken here is to reduce the amount of XIAP produced in cancerous tissue so that apoptosis of diseased cells can take place more readily. Furthermore, it has been shown that XIAP plays a role in gemcitabine resistance and so it is hoped that AEG35156 can also help play a role in enhancing its anticancer activity.

This application was discussed at the April meeting and received a provisional opinion followed by a favourable opinion in August. At the end of August we were notified that

the study would not be commencing and subsequently was closed with no patients recruited.

1.1.4 Prostate Cancer

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

GTAC 154: A phase 1 clinical trial of a replication defective Ad5 vector expressing nitroreductase and GMCSF (AdNRGM) given via brachytherapy, followed by CB1954 in patients with locally relapsed prostate cancer

In this study, a replication defective adenovirus expressing nitroreductase and GMCSF will be given to patients with relapsed prostate cancer. The adenovirus has been modified to produce an immune response. Patients will be treated with brachytherapy, and then receive intravenous CB1954. CB1954 is a prodrug which is converted within the prostate to its active metabolite, which is an alkylating agent. In order to assess the response to therapy, prostatic biopsies will be taken prior to, and one month after injection of the virus into the prostate. The study is dose finding and investigates five different treatment levels. The outcomes that will be assessed include safety, PSA changes and affect upon histopathology.

This application was discussed at the April meeting and received a provisional opinion followed by a favourable opinion in July.

1.1.5 Lung Cancer

There are approximately 37,700 people diagnosed with lung cancer each year. For these patients often the cancer is not found early and has already become malignant (it has spread to other parts of the body). This means that the prognosis for patients with such advanced lung cancer is not good and only around 5% of patients diagnosed with advanced lung cancer have a life expectancy greater than 5 years. There are two main types of lung cancer, non-small cell and small cell lung cancer.

GTAC 155: An ascending dose trial of the safety, tolerability and biological effect of a single intratumoural administration of the selectively replication-competent herpes simplex virus HSV1716 in patients with inoperable malignant pleural mesothelioma

This study will explore primarily the safety and tolerability of HSV1716 administered to patients suffering with pleural mesothelioma, which is a cancer of the layer of tissue found on the outside of your lung. Pleural mesothelioma is a rare tumour, but is of

increasing incidence due mainly to the legacy of exposure to asbestos. HSV1716 is a modified version of the herpes simplex virus (HSV) that causes cold sores. HSV1716 has the potential to destroy cancer cells whilst leaving surrounding normal cells unharmed. This product is well known to GTAC who has reviewed several other studies using this virus.

This application was discussed at the April meeting and received a provisional opinion.

GTAC 156: Registration Phase III study of Lucanix™ (Belagenpumatucel-L) in advanced non-small cell lung cancer: and international multicentre, randomized, double-blind, placebo-controlled study of Lucanix™ maintenance therapy for stages III/IV NSCLC subjects who have responded to or have stable disease following one regimen of front-line, platinum-based combination therapy

This trial is for patients with a specific form of Non Small Cell Lung Cancer called Adenocarcinoma. This type of cancer begins in the cells that line the airways, as do other non small call lung cancers, but in this instance the cancer develops specifically in the type of cells that produce mucus.

TGF-beta 2 (Transforming Growth Factor Beta 2) protein is produced in individuals with lung, and other types of, cancer. It is an immunosuppressive protein, which means that tumour cells, by producing large amounts of this protein, can essentially stop the immune system from mounting an immune response against these cells as they are unable to recognise it as non fully functioning. In particular, high levels of TGF-beta 2 inhibit a group of white blood cells called cytotoxic T cells, which normally act to force tumour (and other 'broken') cells to die.

This is a cell based vaccine made from four different human cell lines which have been isolated and grown from lung tumours. Each of these human cancer cell lines have then been modified by the study plasmid encoding the antisense mRNA version of the TGF-beta 2. This means that the modified cells make less of the TGF-beta 2 protein. The modified human cancer cell lines are irradiated to stop them being able to proliferate in the patient before being injected into patients via the skin (intradermal).

It is hoped that by introducing a vaccine, composed of the four human cancer cell lines with reduced TGF-beta 2 protein expression, that the patients' own immune system will be stimulated to recognise such cells as cancerous and therefore mount an attack not only on the modified cells but also on their own tumour cells.

This application was discussed at the July meeting and given a provisional opinion followed by a favourable opinion in November.

1.2 Infectious Disease

A disease is classed as infectious if it is the direct result of the presence of pathogenic microbial agents such as bacteria, viruses or parasites. Infectious diseases are contagious which means that they can be transmitted from one individual to another or even on occasion between species. A topical example of this would be influenza where there is widespread concern that 'bird flu' may affect humans.

Gene therapy for infectious disease is based upon the creation of a genetic vaccine, which can be based on various different vectors as carriers for the therapeutic gene. The gene usually originates from the pathogen to which a vaccination effect is intended. Its conversion in the body results in the production (called "expression") of a foreign protein (called "antigen") which is hoped may trigger the body to mount an immune attack against the protein - and ultimately against the pathogen. It is hoped that by utilising the benefits of gene therapy it will be possible to prevent infection and create 'cures' for diseases for which currently none exist, for instance, HIV.

1.2.1 HIV

Human Immunodeficiency Virus (HIV) is a retrovirus This means the virus is composed of RNA rather than the more typical DNA. HIV causes AIDS (Acquired Immunodeficiency Syndrome). AIDS develops when the immune system cannot control the HIV virus and begins to fail which leads to many different life threatening illnesses such as rare cancers, pneumonia and TB. Infection in humans is classed as a world-wide pandemic.

HIV is transmitted person to person by three main routes: unprotected sexual intercourse, contaminated blood products and needles, or transmission from mother to baby at birth or from breast milk. The introduction of combination antiretroviral drugs reduces both the mortality and the morbidity of HIV infection but such drugs are not currently available routinely in all countries. Combination antiretroviral drugs are not a cure but aim to control the HIV levels in the blood.

There are two types of HIV that can affect humans HIV-1 and HIV-2. HIV-1 was the first to be discovered. It is more virulent and is the cause of most of the cases of infection as it is easier to transfer.

GTAC 148: A phase 1 randomized double blind placebo controlled trial to evaluate the safety and immunogenicity of TYBC-M4, and *env, gag, tat-rev* and *nef-RT* MVA HIV vaccine and a prime boost regimen with ADVAX, an *env, gag, nef-tat* and *pol* DNA HIV vaccine and TBC-M4

The study proposes to use a vaccine ADVAX which is a mix of two different plasmids (small circular DNA from bacteria) both of which contain HIV-1 genes. The second vaccine is TBC-M4. It too contains HIV-1 genes but is based on a Modified Vaccinia Ankara Virus.

This study is a "prime boost" regime, meaning that the first study product is used to induce an initial immune system response to the virus (prime) and then a second study product is used to enhance that response (boost). The study is also designed to evaluate the immunogenicity of TBC-M4 when combined with ADVAX. It is hoped that this will mean that the patient's immune system will be stimulated against the HIV.

This application was discussed at the February meeting, received approval and full approval was granted in April.

1.2.2 Malaria

Malaria is classed as the most important tropical disease today with somewhere between 300-500 million clinical cases worldwide per year of which there will be somewhere between 1.5-3 million deaths, which puts malaria among the top killers in the world. Ninety per cent of the cases occur in tropical Sahara although the malarial parasite can be found in around 100 countries. A vaccine would be most welcome for malarial treatment, not only for those people living and working there but also for those travelling to the areas of the world where there is a risk of infection.

Malaria is spread between humans through the feeding of the female anopheles mosquito. The female mosquito is infected through biting an affected individual; when the mosquito then feeds on another individual, the parasite can be passed on. Within a very short space of time of a human becoming infected, the parasite will have made its way to liver cells which it enters to reproduce; it can also reproduce within red blood cells. By spending time inside cells, it can evade the body's own immune system.

GTAC 150: Assessment of protection against malaria by sporozoite challenge of healthy adults vaccinated with AdCh63 ME-TRAP and MVA ME-TRAP

This study is the challenge study to GTAC 133 *"A phase I study to assess the safety and immunogenicity of a new candidate malaria vaccine, AdCh63 ME-TRAP alone and with MVA ME-TRAP, using a prime boost delivery schedule".* A challenge study involves exposing study participants to the disease in question in order to determine the effectiveness of the investigational product.

Identical to GTAC 133 are the two investigational products proposed for this study: a vector based on recombinant chimpanzee adenovirus 63 (AdCh63 ME-TRAP), and a vector based on recombinant modified vaccinia virus Ankara (MVA ME-TRAP). Both vectors encode multiple epitopes (a region on the surface of the malaria antigen that elicits an immune response) and the malarial parasite protein Thrombospondin Related Adhesion Protein (TRAP). TRAP is a protein thought to facilitate parasite entry into the liver cells (hepatocytes). In studies involving rodents, immunity to TRAP has shown a high level of immunity to malaria.

This is the first time that the Committee has reviewed a challenge study for malaria. The mosquitoes that will be used in this challenge study have been bred in the laboratory and carry the *falciparum* strain of malaria, which has been shown to be cured by Riamet an antimalarial treatment.

This study was discussed at the February meeting but no opinion was given pending receipt of further information. Full approval was given in October. Subsequently the applicants withdrew this application and submitted a new application with the request that this be transferred under the new arrangements (See Section 1.7)

1.2.3 Influenza

Each winter, the Influenza virus kills around 4,000 people in the UK with the world total at between 500,000 and 1 million generally spreading throughout the world in a seasonal epidemic. Influenza virus affects mainly the upper respiratory tract (nose,

throat and bronchi but rarely the lungs) and the individual remains infectious for about a week. It is an infectious disease of birds (such as the H5N1 strain) and mammals.

GTAC 151: A Phase 1, multicentre, randomised study to assess the immunogenicity and tolerance of a combination regime of trivalent DNA influenza vaccine administered by particle mediated epidermal delivery (PMED) and a standard protein influenza vaccine in healthy elderly adults

The purpose of this study is to determine whether the immune response to a conventional flu vaccine can be improved by giving an experimental DNA flu vaccine either at the same time as or four weeks before the conventional vaccine in healthy subjects aged 60 years and over. Most flu vaccines are given by injection using a needle and syringe. The Sponsor has developed an innovative system for the administration of DNA vaccines. The DNA flu vaccine is made up of very small amounts of genetic material from the flu virus. The DNA is placed on the surface of tiny gold particles, which is delivered into the outside layer of the skin. Once in the skin, the DNA comes off the gold particles, enters the skin cells and other cells. The DNA vaccine is thought to produce an additional immune response (called a cell mediated immune response) as well as an antibody response which may make it more effective than a normal protein vaccine.

This application was discussed at the April meeting when it received a provisional opinion followed by full approval in June.

GTAC 158: A Phase 1/IIa randomised, double-blind, placebo controlled, dose escalating study to evaluate the safety, tolerability, immunogenicity and vaccine-like viral shedding of MEDI-534, a live, attenuated intranasal vaccine against respiratory syncytical virus (RSV) and parinfluenza virus type 3 (PIV3) in healthy 6 to <24 month old children and in 2 month old infants

Infant bronchiolitis (an infectious illness which makes babies wheeze and cough) is the commonest reason a child under a year of age is admitted to hospital in the developed world. Most cases are caused by infection with respiratory syncytial virus (RSV) which is a pneumovirus.

The purpose of this study is to give doses of a new vaccine called MEDI-534 and measure the size of immune response (the body's response to protect against infection) by comparing babies and children who have been given the vaccine with children given a placebo (a dummy vaccine containing no virus). The MEDI-534 vaccine is based on a virus strain (PIV3) that normally infects cows. It also contains a small part of the respiratory syncytial virus (RSV) that cannot grow by itself and does not cause RSV illness. It is hoped that the vaccine may protect infants and young children against these respiratory diseases.

This application was discussed at the October meeting when it received a provisional opinion followed by full approval in December.

1.3 Single Gene Disorders

Much like the name suggests single gene disorders are conditions which are the direct result of a mutation in a single gene. There are about 6,000 known single gene disorders ranging from primary immunodeficiencies (such as the Wiskott-Aldrich study below) to sickle cell anaemia, Huntington's disease, Haemophilia or fragile X syndrome. Single gene disorders occur in around 1 in 200 births, but due to their nature can often be predicted. Single gene disorders generally follow one of a few inheritance patterns, autosomal dominant (where only one copy of the mutated gene is required for an individual to be affected), autosomal recessive (where two copies are required for an individual to be affected, individuals with only one copy are known as 'carriers'), X linked dominant (as the name suggests the mutation is found on the X chromosome, these mutations are quite rare), X linked recessive (also found on the X chromosome therefore they affect far more males than females and are more common than X linked dominant conditions), Y linked (which only affect males as the mutation is found on the Y chromosome alone), and Mitochondrial disease (which is also known as maternal inheritance as only egg mitochondria are found in the developing embryo).

1.3.1 Haemophilia

Haemophilia B is a sex-linked bleeding disorder caused by a deficient clotting factor protein, Factor IX. It affects some 1:30,000-50,000 males and can, on occasion, affect females.

Patients with less than 1-2% factor activity are said to have severe Haemophilia B and experience spontaneous bleeding mainly into knee, elbow and ankle joints, which can cause permanent arthritis and disability if not promptly treated. Patients with moderate haemophilia B have 2-5% factor activity. Those with 5-50% factor activity have a mild form of haemophilia B (normal is classed as between 50 and 200%). These patients will only tend to experience bleeds after major surgery or trauma. Both moderate and mild patient groups only inject themselves when necessary using recombinant Factor IX.

Patients are currently treated with a synthetic type of factor IX called recombinant Factor IX. Using this whenever a bleed occurs means that patients can live normal lives. In cases of severe haemophilia, doctors sometimes recommend giving a regimen of regular factor replacement treatments (a therapy called prophylaxis) to prevent bleeding episodes before they happen.

GTAC 115: An open-label dose-escalation study of a self complementary adeno-associated viral vector (scAAV2/8-LP1-hFIXco) for gene transfer in subjects with hemophilia B

The study proposes to administer a modified adeno-associated virus (AAV) containing the human gene encoding Factor IX (hFIX) into patients who have severe haemophilia B. The treatment will be administered via a peripheral vein this being the safest route for patients who have a severe bleeding disorder. This procedure will be carried out in hospital where patients will be closely monitored for 24 hours.

The vector contains LP1 a liver specific promoter whereby the protein will be produced only in the liver even if the product enters other tissues. There are different subsets of

AAV found in nature that produce a variety of immune system responses in people. These subsets are known as AAV *serotypes*, some of which are more common than others. The serotype to be used in this study is the relatively uncommon AAV8 in an attempt to avoid patients' own immune systems mounting a response against the gene therapy virus before it has a chance to deliver its therapeutic payload.

The Committee originally saw this application in February 2006. A workshop was subsequently held to obtain the views and opinions of physicians and patient group representatives. A number of recommendations from this workshop informed the Committee in requesting the applicants to provide further information and make adjustments to the design of their application. This amended and revised application was discussed at the July meeting when it received a provisional opinion followed by full approval in May 2009.

1.3.2. Wiskott-Aldrich Syndrome

Wiskott-Aldrich Syndrome (WAS) is a primary immunodeficiency disease, a disorder of the immune system, which is seen in between 4-10 births per million and is caused by a mutation on the short arm of the X chromosome. There are many different mutations, which vary in intensity and are unique to either a family or an individual. Where WAS affects a family, the family will have its own specific mutation of WASp (Wiskott-Aldrich Syndrome protein) which can make diagnosis easier. However, around a third of all mutations seen are new spontaneous mutations that occur during conception.

WAS affects the bone marrow and blood, in particular white blood cells. These cells do not work as they should, leaving the individual more open to infections and diseases such as Arthritis and Eczema. It can also lead to a type of cancer called Lymphoma (cancer of the lymph system). Platelets are also affected in individuals with WAS, they are not only fewer in number but are also smaller which can lead to clotting abnormalities.

There is only one current permanent cure for WAS, which as with other primary immunodeficiency, is a bone marrow transplant (and a cord blood stem cell transplant). Unlike X-SCID individuals, those with WAS do have some enduring T lymphocyte function, this means that for a transplant they are required to undergo conditioning by either immunosuppressive drugs and/or total body irradiation. But prognosis is good, for a HLA-identical sibling donor the success rate has reached that of 80-90%. Fully matched unrelated donor transplants are almost as successful if performed when the child is young (generally under 6 years) and before they have acquired a significant complication such as a severe viral infection, however success does decrease with age.

Although there have been advances in the treatment of WAS in recent years it remains a serious disease. Average life expectancy used to be only a couple of years however now, whilst life threatening complications can occur, many affected males reach adulthood.

GTAC 146: Phase I/II clinical trial of haematopoietic stem cell gene therapy for Wiskott-Aldrich Syndrome

This study makes use of a lentiviral vector W1.6hWASPmut6/VSVg. Lentiviral vectors are integrating vectors that have been widely used in the past. It is worth noting that as with other integrating vectors the integration site cannot be predicted. The vector has a number of inbuilt safety features including a self inactivating (SIN) configuration. Using a SIN configuration means that expression of the therapeutic gene is regulated by an internal housekeeping human gene promoter. This means that the vector should have a better safety profile, but this has yet to be definitely proved in the clinic. The other feature that the team claim increases safety is that they are using a haematopoietic specific (blood specific) internal promoter to drive expression of the therapeutic gene.

This will be a first in man for this vector as well as the first time gene therapy has been attempted in this group of patients. It is proposed that the patient's own blood cells will be transduced (the process of transferring the genetic material) in vitro (outside the body) and then reintroduced back into the donor.

This application was discussed at the February meeting when it received a provisional opinion.

1.3.3 Duchenne Muscular Dystrophy

Duchenne Muscular Dystrophy (DMD) is a mostly inherited disease (2/3 of cases) that affects only boys (extremely rarely girls). In the UK, about 100 babies are born with DMD each year with approximately 1,500 known boys living in the UK with the condition at any one time. It is a condition that affects all the muscles of the body causing them to become progressively weaker. Boys with DMD will usually have difficulty walking by age three years, by 13 virtually all will be confined to a wheelchair and by the late teens to early twenties the breathing muscles will be so severely affected that life expectancy is dramatically decreased. Currently there is no cure for DMD.

The wasting of the muscles is caused by an alteration to the gene for a protein called Dystrophin which is an essential component of muscle tissue. As the boys do not produce this protein, new muscle is never created in place of the damaged tissue.

GTAC 157: Dose ranging study of AVI-4658 to induce dystrophin expression in selected Duchenne Muscular Dystrophy patients

This trial proposes to make use of Antisense Oligonucleotides, which are very short pieces of nucleic acid which are designed to bind to a particular section of DNA or RNA, effectively preventing the bound-up part of the gene from being translated into protein. In this study, the antisense oglionucleotides have been designed to get the gene expression machinery of the cell to 'skip' over the mutation in the dystrophin gene. Because of this skipping, production of a mutant protein can be avoided and instead a functional Dystrophin protein is produced. The protein that is made as a result of the skipping is a shorter version. This study will be conducted in young children before too much muscle damage has occurred during their development.

This gene therapy product, called AVI-4658, does not involve the use of a vector. Instead, the investigational medicinal product consists of a short stretch of nucleic acids (known as antisense oligonucleotides) which are delivered directly into the bloodstream. The aim of this study is to determine the safety and dosage level required to elicit at least 10% dystrophin positive fibres and dystrophin production.

This application was discussed at the October meeting when it received a provisional opinion followed by full approval in December.

1.4 Cardiovascular Disease

1.4.1 Peripheral Artery Disease

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

GTAC 099A: Extended follow-up program to GTAC 099 Walk Study

GTAC 99 was approved by the Committee in 2004 and the study has now completed recruitment of participants. It was a study into PAD (Peripheral Arterial Disease) in the leg. Patients were suffering with severe intermittent claudication (muscle pain caused by inadequate blood flow).

The vector was a hypoxia induced factor-1α (HIF-1α). HIF-1α encoded a transcription factor, whose action is to control the expression of other genes. HIF-1α expression itself is upregulated by low oxygen levels in the muscle tissue (hypoxia). When the tissue becomes hypoxic, HIF-1 regulates the expression of a number of other genes which are involved in the cellular response to changes in oxygen levels. These genes encode so-called angiogenic growth factors, which have the ability to stimulate the growth of new blood vessels and potentially increase the flow of oxygenated blood to these cells.

This application is a follow up study for those patients who participated in GTAC 099. The study investigators or the patient's treating doctor will collect information on the participant's health and development of any new cancers or amputations in subsequent years. This observational long term study wishes to contribute to the development of the long-term safety profile of the investigational medicinal product.

This application was discussed at the May meeting and received full approval.

1.5 Stem Cell Transplantation

There are two different types of stem cell transplants: autologous, where the cells are taken from the individual, treated, and then given back to the same individual, and allogeneic (or an allograft) where the cells are from a donor and not the patient himself. In either case, before giving patients their 'new' cells, a very high level of chemotherapy, radiotherapy (or both procedures) is administered to kill the existing (diseased) stem cells that are found in the bone marrow.

With an allogeneic transplant there is an additional risk of Graft versus Host Disease (GvHD) where some of the 'new' white blood cells begin to attack the patient's own cells. This can range from quite mild to very severe and even life threatening. Graft versus Host Disease can also occur where the donor cells not only attack healthy cells but also the remaining cancer cells.

1.5.1 Allogeneic Stem Cell Transplantation

Allogeneic Stem Cell Transplant (SCT) is the only option in seeking a cure for many haematological malignancies. Immune suppression at the time of chemotherapy before SCT and after SCT has helped in the battle against rejection as well as limiting the development of GvHD. However, there is an increased risk of infections following an allogeneic SCT. One of these infections is caused by a commonly occurring virus called adenovirus. Most people in the United Kingdom have been infected by this virus in childhood where it usually causes mild respiratory symptoms (cough/cold/sore throat). After a stem cell transplant adenovirus can produce a serious, and sometimes life-threatening, infection. On detection of adenovirus infection, an antiviral drug is given to try to combat the infection. Unfortunately, none of the current anti-viral drugs efficiently treat adenovirus disease, also they may cause side effects. Adenovirus infection is of particular concern in patients with GvHD. It occurs in between 5 and 20% of individuals after a SCT. Treatment is difficult and thus far antiviral therapies have been of negligible benefit.

GTAC 153: Adoptive immunotherapy for adenovirus (Ad) infection in stem cell transplant recipients

This study is NOT gene therapy. However, the group has previously come to GTAC with similar protocols. This was because the viruses used had been genetically modified.

The immune cells circulating in the donor's blood that control adenovirus infection (anti-adenoviral T cells) are removed and infused into the recipient in an effort to decrease the number of adenoviral particles in the recipient's blood.

The study will use two different methods of selecting the cells. At present, it is not known if one method is better than the other, or if a combination works best. The main aim of this study is to demonstrate that cells can be infused in a safe fashion and that they are effective in combating adenovirus infection.

This application was discussed at the October meeting when it received a provisional opinion followed by full approval in December.

1. 6 Neurological Disorders

A neurological disorder is a disorder that involves the nervous system. A neurological disorder can be caused by either a disease, such as multiple sclerosis, or a trauma or injury to the nervous system. Neurological disorders can be remarkably difficult to treat and are often debilitating.

Symptoms of neurological disorders can include the slow loss of coordination, balance, or ability to speak clearly. Often symptoms start with a mild and intermittent twitching or numbness in one extremity, tremors, rigid muscles, slowed motion, difficulty swallowing, loss of automatic movements such as blinking, swinging the arms, and unconscious acts.

Diagnosing some neurological disorders may very well depend on symptoms evaluation alone. Parkinson's for example, has no definitive test and is more likely to be diagnosed through physical examination well after the initial onset of symptoms.

Treatment options vary greatly depending on the neurological disorder. Some neurological disorders become more difficult to treat as they progress. Physical therapy to retain as much physical dexterity as possible is nearly always prescribed. Medication such as dopamine agonists, Levodopa, carbidopa, selegiline, anticholinergics, or amantadine may help during various stages of neurological diseases. Surgery is an option for candidates who can withstand the surgical process and are able to progress through the physical therapy process. Surgical procedures include the destruction of very small amounts of brain tissue in the affected areas, or the stimulation of various parts of the brain.

1.6.1 Parkinson's Disease

Parkinson's disease (PD) belongs to a group of conditions called motor system disorders, which are the result of the loss of dopamine-producing brain cells in the nigrostriatal system of the brain. The four primary symptoms of PD are tremor (trembling) in hands, arms, legs, jaw, and face, stiffness of the limbs and trunk, slowness of movement; and impaired balance and coordination. As these symptoms become more pronounced, patients may have difficulty walking, talking, or completing other simple tasks. PD usually affects people over the age of 50. Early symptoms of PD are subtle and occur gradually. In some people the disease progresses more quickly than in others.

GTAC 159: A phase II, multicentre, randomized and controlled open-label trial comparing the safety and efficacy of bilateral intraputaminal (IPu) administration of CERE-120 (Adeno-Associated Virus Serotype 2 [AAV2] – Neurturin [NTN]) combined with best medical therapy (BMT) versus BMT alone in subjects with idiopathic Parkinson's Disease

Neurturin (NTN) is a neurotrophic factor which may help maintain neurons (brain cells) in a healthy state. The NTN protein is encoded by the NTN gene. CERE-120 is a genetically engineered adeno-associated virus serotype-2 (AAV2) vector that encodes the human neurturin gene (NTN). By incorporating the NTN gene into an AAV2 vector, it is possible to deliver the NTN gene product to the nigrostriatal system in the brain in

a controlled, sustained, and targeted fashion, thus providing continuous NTN neurotrophic factor to the neurons which are degenerating in PD.

The goal of therapy with CERE-120 is to enhance the function of nigrostriatal dopamine neurons, thereby providing symptomatic improvement of motor function and reduction of "off" time in PD patients. Other important goals of CERE-120 are to protect nigrostriatal neurons from further degeneration and thus slow or prevent disease progression.

This application was discussed at the October meeting when it received a provisional opinion. The study was withdrawn by the applicants in December 2008.

1.7 Transferred Applications

In spring 2008, an amendment to Clinical Trial Regulations came into force which allowed GTAC to transfer an application to a UKECA recognised REC[1] for its ethical review and opinion. GTAC received the following two applications which met the criteria for transfer as they were deemed to be 'low risk' gene therapy.

1.7.1 Unresectable Cancer

GTAC 160-1 A randomized phase III clinical trial to evaluate the efficacy and safety of treatment with OncoVEX^{GM-CSF} compared to subcutaneously administered GM-CSF in previously treated melanoma patients with unresectable stage IIIb, IIIc and IV disease.

This application wished to assess the safety of OncoVEX^{GM-CSF} or GM-CSF only in patients with melanoma. The main study endpoint is to see whether OncoVEX^{GM-CSF} or GM-CSF will destroy these tumours and to assess survival rate.

This investigational medicinal product is well known to GTAC as the Committee had reviewed three previous applications. The first application for a phase 1 study was reviewed in 2001 and since then two further studies have been conducted with small numbers of participants to refine the appropriate dosage and assess the safety and risks of the product.

This application was transferred to the Hammersmith, Queen Charlotte's and Chelsea REC in December 2008.

1.7.2 Malaria

GTAC 160-02 Assessment of protection against malaria by sporozoite challenge of healthy adults vaccinated with AdCh63 ME-TRAP and MVA ME-TRAP MAL034

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1 UKECA recognised REC: "Recognised" means that the REC is entitled to consider clinical trials with investigational medicinal products (IMPs)

This study is the challenge study to GTAC 133 *"A phase I study to assess the safety and immunogenicity of a new candidate malaria vaccine, AdCh63 ME-TRAP alone and with MVA ME-TRAP, using a prime boost delivery schedule".* Identical to GTAC 133 are the two investigational products proposed for this study: a vector based on recombinant chimpanzee adenovirus 63 (AdCh63 ME-TRAP), and a vector based on recombinant modified vaccinia virus Ankara (MVA ME-TRAP). Both vectors encode multiple epitopes (a region on the surface of the malaria antigen that elicits an immune response) and the malarial parasite protein Thrombospondin Related Adhesion Protein (TRAP). TRAP is a protein thought to facilitate parasite entry into the liver cells (hepatocytes). In studies involving rodents, immunity to TRAP has shown a high level of immunity to malaria.

The investigational medicinal product is well known to the Committee and this application which was originally reviewed February (GTAC 150) was transferred to the Oxford REC A in December.

1.8 Amendments to Ongoing Protocols

In 2008, GTAC processed two applications for approval of substantial amendments at Committee meetings. Between Committee meetings over 60 applications for substantial amendments received approval.

SECTION 2: REGULATORY AND GUIDANCE ISSUES

2.1 Public Consultations Considered

In 2008 GTAC discussed and contributed comments to the following seven consultations:

2.1.1 EMEA Ethical Considerations for Clinical Trials on Medicinal Products conducted with Paediatric Population

The EMEA have issued recommendations of the ad hoc group relating to good clinical practice in the conduct of clinical trials on children. The document provides recommendations on various ethical aspects of clinical trials performed in children from birth up to the legal age of adulthood.
The Committee discussed the content of these recommendations at the April meeting and welcomed the aspiration of the document to give appropriate ethical guidance on treating children participating in research throughout Europe.

2.1.2 EMEA Guideline on safety and efficacy follow-up – risk management of advance therapy medicinal products

EMEA have issued a consultation paper on Safety and Efficacy follow-up risk management of Advanced Therapy Medicinal Products (ATMPs), which include authorised gene therapies.

This guideline describes specific aspects of pharmacovigilance, risk management planning, safety and efficacy follow-up of authorised ATMPs as well as some aspects of clinical follow-up of patients treated with such products.

Committee members commented on these guidelines at the July meeting.

2.1.3 EMEA Guideline on follow-up of patients administered with gene therapy medicinal products

This proposed guideline addresses the principles for the follow-up of patients administered with a gene therapy medicinal product as well as those enrolled in gene therapy clinical trials.

The nature of the follow-up recommendations vary depending on the risk profile of the gene therapy approach by taking into account the specifics of the gene therapy medicinal products and of the transfer vector, the disease, co-morbidity and the patient target population.

Committee members discussed and commented on this guideline at the July meeting.

2.1.4 Consultation - Review of the World Medical Association Declaration of Helsinki

The World Medical Association (WMA) has issued a consultation on a draft revision of the Declaration of Helsinki.

The proposed amendments were noted at the July meeting.

2.1.5 Consultation - Guidance to Doctors on Obtaining Consent for Research

At the July meeting the Committee noted the content of the call for comments by the General Medical Council to their proposed guidance paper on obtaining consent for research.

It was requested that comments were sent to the Secretariat in order that a collective response on behalf of the Committee could be given.

2.1.6 MHRA Consultation on Advanced Therapy Medicinal Products - Exemption Scheme

Members noted that MHRA were requesting comments on the proposal for an exemption scheme to cover advance therapy medicinal products, which are prepared on a non-routine basis and used in the same hospital.

At the October meeting Members were asked if they had any particular comments with regards to point 21 of the document, which states that GTAC could be called to give advice in its role as a Ministerial Advisory Committee.

2.1.7 NHS Connecting for Health – Additional uses of Patient Data.

At the October meeting Members were asked to note that NHS Connecting for Health were consulting with stakeholders on how patient information held by the NHS could be used for additional purposes.

2.2 Regulatory issues specific to GTAC

2.2.1 GTAC Standard Operating Procedures (Parent SOPs) and GTAC Supplementary Operating Procedures (Transfer SOPs)

GTAC's role under the Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008 changed when the amended Regulations came into force on 1 May 2008. The amendments, as they relate to the role of GTAC under the Regulations, enabled the Committee to delegate applications with "low risk" gene therapy products to one of three recognised flagged NHS RECs. This coincided with a change to GTAC's Terms of Reference giving GTAC a role in considering certain stem cell applications (namely those with products derived from stem cell lines).

GTAC's main SOPs (called the parent SOPs) setting out the practices and procedures to meet its obligations as a Research Ethics Committee together with a copy of the Supplementary Operational Procedures covering the transfer of applications were issued on 01 May 2008.

Both documents are available on the GTAC website at:
http://www.dh.gov.uk/ab/GTAC/AboutGTAC/index.htm

2.2.2 GTAC New Terms of Reference

In order to coincide with amended Clinical Trials Regulations which came into force on 01 May 2008 GTAC's Terms of Reference were also amended to incorporate their new role in overseeing stem cell research.

The Terms of Reference are posted on the GTAC website at :
http://www.dh.gov.uk/ab/GTAC/AboutGTAC/index.htm

- 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.
- To consider and advise on the acceptability of proposals for research on human subjects using cells derived from stem cell lines, based on ethical grounds, taking account of the scientific merits of the proposals and the potential benefits and risks.
- To provide ethical advice on the use of unlicensed gene therapy and stem cell line derived therapies in humans.
- To work with other agencies which have responsibilities in this field, including research ethics committees, and agencies with statutory responsibilities - the Medicines and Healthcare products Regulatory Agency, the Human Tissue Authority, the Health and Safety Executive and the Department for Environment Food and Rural Affairs.
- To provide advice to United Kingdom Health Ministers on the above matters.

2.2.3 Adoption of Integrated Research Application System (IRAS) Form for GTAC Applications

This year has also seen the adoption of a new GTAC application form based in an online system called IRAS (Integrated Research Application System).

Applicants need only complete one form for making research applications to up to seven individual bodies: GTAC, RECs, MHRA, R&D, UKCRC, ARSAC and PIAG. This will substantially reduce duplication of data-input by applicants and streamline the process.

From GTAC's perspective it means that the GTAC application form will be phased out in preference of using the common IRAS form for all applications to the Committee.

SECTION 3: MEETINGS AND WORKSHOPS

3.1 Workshop on transferring applications – 29 January 2008

In preparation for the implementation of the Amendments to the Clinical Trials Regulations which came into effect in May GTAC hosted a workshop at the beginning of the year.

The workshop comprised a number of GTAC members, key GTAC stakeholders and experts in gene therapy to decide which 'routine' gene therapy trials would be suitable for delegation to another NHS REC.

The intention is to enable some applications that currently come to GTAC to be delegated to another designated NHS REC thereby creating the necessary resources so that GTAC can act on the Government's wish for it to review other forthcoming research (eg stem cells) and also spend more time on its role as an advisory body.

The group was supportive of the concept of transfer of certain applications for gene therapy clinical trials to a suitable NHS REC and their input was valuable in creating the 'decision tree' which will assist researchers in deciding whether their application meets the criteria for transfer.

The 'decision tree' is available on the GTAC website at:
www.dh.gov.uk/ab/GTAC/Applications/index.htm

3.2 Training Day for flagged Research Ethics Committees undertaking transferred applications – 28 April 2008

A training day was held on 28 April 2008 with the three RECs that have been flagged to review those 'low risk' gene therapy studies that meet GTAC's criteria for transfer.

The event was attended by many GTAC Committee members together with representatives from the National Research Ethics Service (NRES) and the Chairs and members from the three RECS who have been nominated to receive transferred applications.

Each of the three speakers gave a very descriptive presentation to illustrate the type of applications that would be suitable for transfer to the flagged RECs. The afternoon finished with an in depth question and answer session.

3.3 British Society For Gene Therapy (BSGT) Conference

The 2008 Public Day and Scientific Conference was held in Edinburgh's Heriot-Watt University on 7-9 April. Several Committee members gave presentations

at the Conference whose aim is to improve the public and media perception and understanding of gene and cell therapy.

On 7 April BSGT and GTAC co-hosted a public engagement day. The event gave attendees an opportunity to discuss and debate gene and cell therapy research with scientists, patients, journalists and clinicians, and to think about the impact that the research has on society and themselves.

3.4 Horizon Scanning – Gene Therapy

3.4.1 Presentation on the latest state of the art / horizon scanning for gene therapy

At the December meeting Prof Len Seymour gave a presentation from the British Society for Gene Therapy's (BSGT'S) perspective of both current gene therapy clinical trials and those areas to be investigated in the foreseeable future.

Following the presentation discussion centred on the difficulties experienced by researchers in bringing their research to the clinic. In the current economic climate, researchers found that both obtaining funding support and the regulatory requirements of producing vectors to Good Manufacturing Practice (GMP) standards were increasingly a challenge.

3.5 Horizon Scanning – Stem Cells

3.5.1 Presentation on Stem Cells, Regenerative Medicine and UK Governance Arrangements

The change to the Clinical Trials Regulations enables GTAC to fulfil its new responsibilities within its Terms of Reference as a Ministerial Advisory Committee to advise on clinical trials involving cell therapies derived from stem cell lines.

Therefore on 16 July Committee members were given a contemporary overview of the UK Governance arrangements for the generation, storage and use of stem cell lines in order to be updated on the current regulatory landscape requirements for the use of stem cell lines in research.

Five speakers including representatives from the Human Fertilisation and Embryology Authority, Human Tissue Authority and the Medical Research Council gave presentations to the Committee on the UK regulatory system overseeing stem cell research. This was followed by a question and answer session at the end of the afternoon.

3.5.2 Presentation on Stem Cell Research for Blindness

At the December meeting Prof Pete Coffey who is a Director of the London Project to Cure Blindness gave the Committee a presentation on the current developments in stem cell research into blindness using his own experiences as a basis for discussion. He gave details on how his project is progressing and described some of the issues that had to be overcome to move the project closer to the clinic.

SECTION 4: UPDATE OF CLOSED UK CLINICAL TRIALS

The following are short summaries provided by researchers of gene therapy trials that have closed. GTAC would like to thank all researchers who have contributed to this section, which builds on initiatives in previous reports. The summaries are essentially unedited and reflect the views of the researchers.

4.1 Single Gene Disorders

4.1.1 GTAC 045: Phase I clinical gene therapy protocol for X-SCID

Introduction:
This was a phase I/II open label study of gene therapy in the disorder X-linked severe combined immunodeficiency (X-SCID). X-SCID is a genetic disorder that affects boys. It is caused by errors in a gene that leads to a deficiency in cells known as lymphocytes. Lymphocytes are cells of the immune system and are crucial for protection against infection. Common infections, which have little effect on normal individuals, can therefore have severe consequences in X-SCID. Although some protection can be provided by drugs such as antibiotics and antibodies, this disease is usually fatal within the first few years of life. Fortunately, X-SCID can be cured by bone marrow transplantation. The chances of success are very good (over 90%) when a fully matched family donor is available. However, only a third of patients have a fully matched donor and the chances of success from other donor sources donors are significantly worse (about 60%) and they suffer side effects due to the treatment required to prepare the patient for transplant. Alternative treatments that have fewer side effects are highly desirable.

Objective:
The purpose of this study is to determine whether the bone marrow cells can be given a correct version of the faulty gene and produce enough lymphocytes in the blood to protect against infection. It will also determine how long the effect will last, and whether the procedure is safe.

Recruitment:
A total of 11 were patients enrolled over a period of 6 years (from 19/07/2001 to 12/05/07). All patients were eligible because they did not have a good bone marrow donor.

Results and conclusions:
Clinical response has been excellent in all ten children treated, and all were able to return home and resume normal lives including schooling and interaction with other children. In one adult patient treated following a partially effective transplant as a child, there was no improvement because it is more difficult to make new immune cells in older children and adults. One patient in the trial developed leukaemia as a result of the gene therapy. Fortunately, he has responded well to chemotherapy, and is currently healthy. Overall this trial has shown that gene therapy is remarkably effective at treating SCID, but that modifications in the gene medicine should be made to improve safety. These changes are likely to be tested in new trials in 2009.

4.2 Cardiovascular Disease

4.2.1 GTAC 54: A Phase II, Randomised, Double-Blind, Placebo-Controlled, Parallel Group, Efficacy and Safety Study of NV1FGF in Patients with Severe Peripheral Artery Occlusive Disease

For patients with severe peripheral artery occlusive disease (Critical Limb Ischaemia), the current available treatments include vascular surgery and/or balloon dilatation of arteries (angioplasty). However, in some cases, such treatment may not be possible or successful and some form of amputation might be required.

This study was done to look at the possibility of a treatment that will avoid amputations in patients not suitable for standard treatment by using a new gene therapy medication, named NV1FGF.

NV1FGF is fibroblast growth factor protein which stimulates the growth of blood vessels. The purpose of this study was to determine if NV1FGF is safe and effective in the formation of new blood vessels in legs where the arteries are blocked, compared with a placebo (dummy medication).

This research study was done in six European countries from 2002 to 2005 and a total of 125 eligible patients (including 11 patients from the UK) were included in the study. These patients were scheduled to receive eight intramuscular injections of placebo or NV1FGF on four treatment occasions.

In this study, the treatment with NV1FGF was found to be well tolerated and the occurrence of side effects were similar between the two groups who received NV1FGF or placebo. The results from 107 patients were judged to be eligible for analysis.

Although it was found that the improvements in ulcer healing were similar in patients who were treated with NV1FGF (19.6%) or placebo (14.3%), it was also found that the use of NVIFGF significantly reduced (by twofold) the risk of all amputations and major amputations. Furthermore, there was also a trend for reduced risk of death with the use of NV1FGF in this study.

The results from this study indicate that treatment with NV1FGF may offer the potential for effective treatment of patients suffering from Critical Limb Ischaemia and have provided the basis for performing a further phase III research study which is currently performed world-wide (TAMARIS: Therapeutic Angiogenesis for the Management of Arteriopathy in a Randomized International Study).

The original full article was published in the American Society of Gene Therapy, www.moleculartherapy.org vol 16, no 5, 972-978, May 2008.

4.3 Infectious Disease

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

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

The analysis of this completed study was published in Vaccine (2008) Volume 26, 3162-3174. In summary the study concluded that of the 35 participates that completed the regimen 90% (18/20) in the DNA C group had ELISpot responses compared to 33% (5/15) that received NYVAC C alone. The vaccine was well tolerated and these promising results suggest that DNA C was an effective priming agent that merits further investigation.

4.4 Cancer

4.4.1 GTAC 87: A Phase II Study Immunologically Evaluating 5T4-MVA (TroVax) in Patient Undergoing Surgical Resection of Colorectal Liver Metastases

Study Opened to recruitment: 10th June 2004
Last Patient Last Visit: 2nd November 2006
Total of 20pts recruited

Introduction

The human oncofetal antigen 5T4 is a surface glycoprotein expressed by placental tissue but also by a wide range of human carcinomas including most colorectal and renal carcinomas. It has limited, weak expression by normal tissue. Administration of a vaccine construct utilising a Modified Vaccinia Ankara (MVA) vector to deliver 5T4 has been shown to generate immune responses in late-stage colorectal cancer patients in a phase I/II trial.

This trial sought to investigate the immunological effects of the vaccine (MVA-5T4, TroVax®) both in the peripheral blood and tumour resected during potentially curative surgery for colorectal cancer liver metastases.
The group of patients selected had a good performance status and may have micrometastatic disease persisting post-operatively. In this setting of low tumour burden immunotherapy is more likely to be efficacious.

Methods
Colorectal cancer patients selected for resection of liver metastases were offered entry to the trial. Following screening patients received 2 vaccinations at intervals pre-operatively and 2 post-operatively. CT scans were performed pre- and post-operatively as routine practice. Surgery occurred at week 4. Blood samples were taken for routine investigations and immunological assays at screening and 2 weeks after each vaccination. A tumour biopsy was obtained at surgery. Immunological responses were assessed using assays performed at 2 centres: Primary assays at Oxford Biomedica (OBM) Plc, Oxford and secondary assays at The Paterson Institute for Cancer Research (PICR), Manchester.

Immunohistochemical analysis, performed at PICR, was used to confirm tumour antigen expression and the nature of T-cell infiltration into the liver. T-cell responses were measured using proliferation assays and gamma-interferon ELISPOT. Antibody responses were assessed using ELISA. If evidence of an immunological response to the vaccination was demonstrated the patients were offered 2 further vaccinations at later timepoints.

Clinical Outcomes
20 patients were recruited, all evaluated for toxicity. 17 received at least 4 vaccines. 4 excluded from final trial analysis: 1 incorrect diagnosis (hepatocellular carcinoma), 3 inoperable liver metastases. No grade III or IV toxicity related to vaccination. Mild injection site reactions or flu-like symptoms were recorded.

Results summary
Of 20 patients recruited, 16 had successful surgical resection of colorectal cancer liver metastases. No grade III or IV toxicities were seen in relation to vaccination. 5T4 expression was seen in 18 of 18 tumours, CEA in 19 of 19. There was no HLA class I or II down-regulation.

12 patients had new or boosted T-cell responses to 5T4 following vaccination. 17 patients had 5T4-specific antibody responses following vaccination. Most patients developed strong T-cell and antibody responses to the vector MVA.

Conclusion
This study demonstrated that:

- In patients with colorectal cancer liver metastases, the administration of TroVax was well tolerated in the neoadjuvant and adjuvant setting. Local injection site reactions and mild flu-like symptoms were the main toxicities.
- 5T4 expression was positive in the majority of colorectal cancer liver metastases confirming the utility of this antigen as a target for immunotherapy.
- CD3 cells accumulated in peritumoural areas within the liver. CD4 cells predominated over CD8.
- T-cell responses to 5T4 were induced within a short pre-operative period of only 4 weeks in a significant proportion of patients, and antibody responses in the majority.
- In a longer post-operative adjuvant setting most patients mounted positive 5T4-specific T-cell and antibody responses.

The potential clinical benefits of this strategy cannot be reliably assessed in a study of this size.

4.4.2 GTAC 090: A Controlled, Randomised, Parallel Group Study Of The Efficacy And Safety Of Herpes Simplex Virus – Thymidine Kinase Gene Therapy (Cerepro) with Subsequent Ganciclovir For The Treatment Of Patients With Operable High-Grade Glioma

Cerepro is an adenovirus (similar to the virus that causes the common cold) which has been chemically altered to produce a protein called thymidine kinase. Thymidine kinase can activate Ganciclovir to initiate the killing of actively dividing tumour cells. Treatment with Cerepro involves the injection of Cerepro directly into the wound bed in the brain following surgical removal of the tumour. Five days after surgery a 14-day course of Ganciclovir is begun. In this study, two hundred and fifty-one patients were randomised at 38 sites in 9 countries as summarised in the table below:

Country	Number of Sites	**Number of Patients enrolled per country**
Belgium	3	13
Czech Republic	3	17
Finland	3	9
France	5	27
Germany	9	52
Hungary	3	7
Israel	5	56
Poland	5	65
UK	2	5
Total	38 sites	251 patients

Patients were randomised to Cerepro on top of Standard Care, or Standard Care alone. Standard Care included surgery plus radiotherapy and at the discretion of the physician, temozolomide use was permitted.

The primary endpoint of this study was time to death or re-intervention (surgery, radiotherapy or chemotherapy). In a disease such a glioma where the prognosis is poor, this was considered a clinically relevant endpoint as patients frequently may have re-interventions to prolong life. The principal secondary endpoint was all-cause mortality and safety assessments were made throughout the study. Additional blood and in some cases throat swab samples were taken to monitor any shedding of the virus or any increase in the levels of anti-adenovirus antibodies.

The safety profile of Cerepro is consistent with that expected of a local therapy with events being mainly localised in the central nervous system. No shedding of virus was found in throat swab samples and very limited, generally unquantifiable biodistribution of Cerepro was seen. An increase in anti-adenoviral antibodies was found in patients treated with Cerepro but levels declined after Day 19 and no correlation was found with any safety parameter.

One difficulty highlighted in this study was the large variation in time taken to obtain protocol amendment approval. The first site approval for one amendment was obtained within one month of submission and the last site approval took almost 26

months. A degree of variation in obtaining approval is expected but the extent of difference in this case was extremely difficult to manage.

In terms of recruitment, one disappointment was the low number of patients recruited in the UK. Only two sites actively recruited patients; one inactive UK site had to be closed.

4.4.3 GTAC 126: A phase II study of the Efficacy, Safety and Immunogencity of OncoVEX in Patients with Stage IIIc and Stage IV Malignant Melanoma. EudraCT: 2006-003841-17

The OncoVEX$^{GM\text{-}CSF}$ vector is a conditionally replication competent herpes simplex type-1 virus used for the treatment of solid tumours. The vector also contains the coding sequence for human GM-CSF, a cytokine involved in the stimulation of immune responses.

In this study a single dose was selected to evaluate tumour response (assessed via CT and/or PET-CT, clinical measurements and tumor biopsies) and median survival in patients that underwent direct intratumoral injections into one or more cutaneous or subcutaneous tumors. Up to 24 injections separated by a period of two weeks were to be given and patients were to be followed for survival until study completion. Study completion was defined as 6 monts after the last subject received the last dose of study treatment.

As of 24 December 2008 a total of 50 patients have been enrolled and treated in the study, while 29 remain in long term follow-up for survival. The trial was closed for active treatment at eight clinical sites; seven in the Unites States and one in the United Kingdom. Five sites in the US remain open with patients in long term follow-up. The study's long term follow-up will be completed in April of 2009.

The most frequent occurring adverse events were fever, chills, nausea, fatigue, vomiting and headache. There is evidence that both injected and distant uninjected lesions regressed after treatment with OncoVEX$^{GM\text{-}CSF}$. Thirteen patients demonstrated an objective response of whom eight had complete response (CRs) and vie had partial responses (PRs).

SECTION 5: ANNEXES

ANNEX A: GTAC MEMBERS AND ATTENDEES IN 2008

- Professor Martin Gore (Chairman), Consultant Medical Oncologist, The Royal Marsden Hospital, London.
- Dr Richard Ashcroft, Medical Ethicist, Barts and the London.
- Professor Andrew Baker, Professor of Molecular Medicine, University of Glasgow.
- Dr Kathleen Bamford, Consultant Medical Microbiologist and Visiting Professor, Imperial College Healthcare NHS Trust and Imperial College
- Mrs Deborah Beirne, Senior Research Nurse, St. James Hospital, Leeds.
- Professor Hilary Calvert, Professor of Medical Oncology and Clinical Director of the Northern Institute for Cancer Research, University of Newcastle Upon Tyne.
- Professor Mary Collins, Division of Infection and Immunity, Royal Free and University College Medical School.
- Ms Claire Foster, Policy Adviser, Medical Ethics, Archbishops' Council.
- Professor Terence Hamblin, Professor of Immunohaematology, University of Southampton; Consultant Haematologist with Southampton University Hospitals and Kings College Hospital, London.
- Dr Peter Harris, CMO, Algeta
- Professor David Harrison (Vice Chairman), Professor of Pathology and Medical Researcher, Department of Pathology, Edinburgh University.
- Mr Michael Harrison (Alternate Vice Chairman), Barrister, London.
- Professor Nicholas Lemoine, Professor of Molecular Pathology, Institute of Cancer, Queen Mary University of London (until April 2008).
- Dr Adrian Lepper, Chartered Engineer, Hertfordshire.
- Dr Stephen Minger, Director, Stem Cell Biology Laboratory, Wolfson Centre for Age-Related Disease, KCL, London.
- Right Reverend Dr Lee Rayfield, Bishop of Swindon and former immunologist.
- Mrs Fiona Sandford, Patient Advocate, Hertfordshire.
- Dr Michael Waterhouse, Television Producer and Author, Southborough.

Co-opted Members

- Dr Jonathan Grigg, Barts and the London Hospital, London (October meeting to advise on a Duchenne Muscular Dystrophy application and the vaccine against respiratory syncytical virus (RSV) and parainfluenza virus type 3 (PIV3) in healthy children and infants).

- Dr Angela Thomas, Royal Hospital for Sick Children, Edinburgh (February meeting to advise on the Wisckott Aldrich Syndrome application).

- Dr Adrian Thrasher, Great Ormond Street Hospital, London (April meeting to advise on the Adoptive Immunotherapy for Adenovirus Infection in Stem Cell Transplant Recipients application and to contribute to the discussion on the recommendations issued by EMEA for Clinical Trials on Medicinal Products Conducted with Paediatric Population).

Observers

Medicines and Healthcare products Regulatory Agency (MHRA):

- Dr Riaz Zuhrie

Health and Safety Executive:

- Dr David Brown
- Dr Susan Grogan
- Dr Paul Logan
- Dr Michael Paton

Secretariat (Department of Health)

- Dr John Connolly
- Ms Joanna Edwards
- Ms Mamta Malhotra-Bajaj
- Mrs Halina Pounds
- Dr Monika Preuss

Payment of members

Fees are payable to Members at a rate of £148.59 per meeting, £180.40 per meeting for the Chair, and members are reimbursed for all reasonable travelling expenses.

ANNEX B: MEMBERS' ATTENDANCE IN 2008

Name	Meetings attended in 2008
Professor Martin Gore	February, April, July, October, December
Professor David Harrison	April, July, October, December
Mr Michael Harrison	April, July, October (from Item 5.0),
Professor Richard Ashcroft	February (from item 4.0), April, July, October, December
Professor Andrew Baker	February (from item 8.0), April, July, October, December
Dr Kathleen Bamford	February, April, July (from item 6.0), October, December
Ms Deborah Beirne	February, April, July, October, December
Professor Hilary Calvert	February, April, July, October, December
Professor Mary Collins	February, April, July, October, December (from item 5.0)
Ms Claire Foster	February, April, October, December
Professor Terry Hamblin	February, April, July, October,
Dr Peter Harris	February, April, July, December
Professor Nick Lemoine	February, April, December
Dr Adrian Lepper	February, April, July, October, December
Dr Stephen Minger	February, April, July, December (from item 8.0)
Bishop Dr Lee Rayfield	February (from item 5.0), April, October, December
Mrs Fiona Sandford	February, April, July, December
Dr Michael Waterhouse	February, July, October, December

ANNEX C: REGISTER OF MEMBERS INTERESTS IN 2008

GTAC MEMBER	DECLARED INTEREST
Dr Richard Ashcroft	Director of the Appointing Authority for Phase I Ethics Committees (AAPEC) (mid 2008)
Professor Andrew Baker	None
Dr Kathleen Bamford	Chair HHT Gene therapy and genetic modification safety committee Companies who have paid expenses or provided financial support for attendance at meetings, or paid honoraria include Pfizer/Pharmacia Ltd, Gilead Ltd, Wyeth Ltd, Bayer Ltd, Baxter. Research funding: Pfizer Advisory boards: Pfizer, Baxter Fundraising committee: International Child Care Trust
Mrs Deborah Beirne	Post is supported by Cancer Research UK Work involves gene therapy trials
Professor Hilary Calvert	Occasional Advisory boards for: Novartis, GSK, Schering AG, Nerviano Pharmaceuticals, Kudos Pharmaceuticals/AstraZeneca, Eli Lilly, Schering Plough Research grants to Prof Calvert/the Department from: Eli Lilly, Pfizer, OSI
Professor Mary Collins	None
Ms Claire M Foster	None
Professor Martin Gore	Companies who have paid honorariums, expenses and financial support of clinical trials and research include: Cobra Therapeutics Ltd., Genta Inc., ML Laboratoties PLC, Onyx Advisory Board of Onyx Advisor to Cambridge Antibody Technology
Professor Terence Hamblin	Ad hoc consultant to Genzyme and Protherics Paid employment as Editor of Leukemia Research by Elsevier Publications
Dr Peter Harris	Algeta ASA (share option holder) Ad hoc consultant to Crusade Laboratories Ad hoc consultant to Spirogen Ltd
Professor David Harrison	Consultancies: University of Florida; The Forensic Institute; Crusade Laboratories (dormant); Director, Edinburgh Cancer Research UK Clinical Centre Shareholdings: The Forensic Institute Chair, EMMS Nazareth (overseas healthcare charity),

	unpaid; Director, Emmanuel Healthcare (overseas healthcare charity), unpaid Indirect support: Research funds from CRUK, MRC, Wellcome Trust, Chief Scientist Office, Scotland
Mr Michael Harrison	Managing director of Bioethics Consulting Ltd. (dormant) Independent practising barrister working in the field, interests are declared as appropriate
Professor Nicholas Lemoine	Consultant for Medical Solutions Ltd. Joint project funding for gene therapy agent with Cronos Therapeutics Limited from CR-UK Development Fund. Co-investigator on trial protocol with an agent from BioVex Limited
Dr Adrian Lepper	Secretary to the Board, eLearning Holding company Member of Corporation and Governor, West Herts College Independent consultancy assignments Chair of Trustees - Care Co-ordination Network (UK) Wife has a small shareholding in Glaxo Smith Kline
Dr Stephen Minger	PhD studentships jointly funded by GSK/MRC and Novartis/MRC, received honoraria for research seminars from GSK, Novartis, Merck Co-Organiser of London Regenerative Medicine Network which is partially funded by GSK Member of Progress Educational Trust Advisory Panel Paid consultant to Vertex Pharmaceutical Company (fees placed into research accounts) Unpaid advisor to Nikon Corp.
Bishop Dr Lee Rayfield	None
Mrs Fiona Sandford	None
Dr Michael Waterhouse	None

ANNEX D: EXTERNAL EXPERT ADVISERS TO GTAC IN 2008

GTAC is extremely grateful to all its expert advisers for their support in the review of applications and for their input of expertise and advice in 2008. These included:

Prof Robin Ali, University College London

Prof Roger Barker, Cambridge Centre for Brain Repair

Prof Finbarr Cotter, Barts and the London

Dr Lucy Dorrell, John Radcliffe Hospital, Oxford

Prof Farzin Farzaneh, King's College London

Prof Duncan Geddes, Royal Brompton Hospital, London

Professor Brian Greenwood , London School of Hygiene and Tropical Medicine

Prof Peter Jenner, Kings College London

Dr Christoph Klein, Medical School, Hanover, Germany

Dr David Landau, Guy's Hospital, London

Prof Christine Lee, University of London

Dr Tim Lee, St James's University Hospital, Leeds

Prof Matthias Lohr, Karolinski Institutet, Stockholm, Sweden

Prof Norman Maitland, University of York

Dr Emma Morris, Royal Free Hospital, London

Prof Paul Moss, University of Birmingham

Prof Jim Neil, University of Glasgow

Dr Dairmuid O'Donnell, Addenbrooke's Hospital, Cambridge

Dr Christian Ottensmeier, Southampton General Hospital

Prof Terry Partridge at the Centre for Genetic Medicine Research, George Washington University, Washington USA

Dr Jim Robertson, National Institute for Biological Standards and Control (NIBSC), Potters Bar, Herts

Dr Dominic Ruettinger, Munich University, Germany

Dr Jonathan Stoye, National Institute of Medical Research, London

Dr Gordon Taylor, University of Bath

Dr Robin Thorpe, National Institute for Biological Standards and Control (NIBSC), Potters Bar, Herts

Prof Adrian Thrasher, Great Ormond Street Hospital, London

Prof Jonathan Waxman, Hammersmith Hospital, London

Prof Keith Wheatley, University of Birmingham

Dr Yuan Zhao, National Institute for Biological Standards and Control (NIBSC), Herts

ANNEX E: SUMMARY OF UK GENE THERAPY CLINICAL RESEARCH 1993 - 2008

A table summarising all the research applications which have been reviewed by GTAC is available on the GTAC website at:
http://www.dh.gov.uk/ab/GTAC/Publications/index.htm