Annual report : 1995 / Gene Therapy Advisory Committee.

GENE THERAPY ADVISORY COMMITTEE

SECOND ANNUAL REPORT

JANUARY 1995 – DECEMBER 1995

Health Departments of the United Kingdom
May 1996

The GTAC Secretariat may be contacted at:

Department of Health
Room 401
Wellington House
133-155 Waterloo Road
LONDON SE1 8UG

Tel: 0171-972 4021
Fax: 0171-972 4196

FOREWORD

The first annual report of the Gene Therapy Advisory Committee (GTAC), published[1] in 1995, was widely welcomed as an important means of ensuring that accurate information about gene therapy trials in the United Kingdom was placed in the public domain.

The current report describes the consolidation of GTAC activities in the second full year of the Committee's work. Although the number of new protocols submitted for review was lower than in 1994, the range of disorders in which gene therapy research has reached the stage of early clinical trials widened. During 1995 the Committee particularly noted the addition of another inherited single gene disorder, Hurler's Syndrome, to the list. From the level of funding of pre-clinical research in gene therapy it is likely that GTAC can expect to see more clinical scientists coming forward with trials over the next two to three years, although the complexities and difficulties of the subject indicate diligent progress.

The Committee has issued its second piece of guidance to the research community. "Writing Information Leaflets for Patients Participating in Gene Therapy Research" was published in August 1995[2] and draws attention to an area that GTAC highlighted as a priority in its first annual report. The Committee is pleased to note that the guidance has been welcomed.

The annual reports of the Committee are intended to make a continuing and important contribution to the greater dissemination of information about gene therapy research. GTAC is nevertheless anxious to further public comprehension and awareness in this area and has agreed to several initiatives including the issue of press releases, the production of public consultation documents and the holding of workshops.

The Committee said farewell to three members last December. Professor Martin Bobrow, Mr. Nick Ross and Professor Robin Weiss served first on the Clothier Committee from 1989 to 1993 and subsequently on GTAC. They made important contributions to establishing the framework on which the Committee now operates. They gave freely of their time, and their talents greatly enhanced our meetings. I am most grateful to them for all they have done.

Professor Dame June Lloyd
May 1996

CONTENTS

ANNEXES

SECTION 1 - PROTOCOLS CONSIDERED BY GTAC (1995)

1.1 GTAC met three times during 1995 and received a total of six protocols for review. The Committee was content in principle, subject to conditions, for three protocols for *gene therapy** research in human subjects to proceed; two protocols were still under consideration at the time of this report. The remaining protocol was withdrawn at the request of the proposers and is expected to be resubmitted during 1996.

1.2 In total, since 1993, GTAC and its predecessor, the Clothier Committee, have completed the review of research protocols for the following diseases: severe combined immunodeficiency (1), cystic fibrosis (4), malignant melanoma (2), lymphoma (2), neuroblastoma (1), breast cancer (1), Hurler's syndrome (1) and cancer of the cervix (1). In addition, protocols have been submitted for studies in neck and head cancer and in acute myeloid leukaemia.

1.3 Progress in three areas is reviewed in the following paragraphs.

BREAST CANCER

1.4 One in twelve women currently develop breast cancer. The UK has one of the highest death rates from this disease in the world. The majority of the patients present with a breast lump which is removed surgically and the remaining breast tissue is then irradiated. Whilst this treatment is usually effective in dealing with the primary tumour, some 70% of patients develop *metastases* within 10 years. To reduce that problem extensive studies of chemotherapy and hormonal manipulation have been performed.

1.5 The treatment of *metastatic* breast cancer initially involves the use of hormonal drugs. Unfortunately the overall complete response rate of advanced disease to hormonal medication is about 30% with the majority of patients relapsing within two years. Chemotherapy is essentially *palliative* with little prolongation of survival despite promising initial responses.

1.6 There has been almost no change in the survival rate of patients with metastatic breast cancer over the last two decades despite the development of a significant number of anti-cancer agents; the emergence of drug resistance and toxicity to high doses is an undoubted problem in those patients who have initially had a good response. The research described is an attempt to overcome this problem.

Genetic prodrug activation therapy for breast cancer – a phase I study. Department of Clinical Oncology, Royal Postgraduate Medical School, Hammersmith Hospital, London

1.7 Advances made in the understanding of the mechanisms of tumour formation suggest fundamental differences between normal and cancer cells. *Prodrug* activation is a novel, genetically based cancer therapy which seeks to exploit these differences to increase the specificity of the anti-cancer drug treatment. A prodrug compound when administered to a patient has limited or no activity before being converted within the body to its active form. Prodrugs are of great interest in cancer. If the conversion to active drug can be restricted to the target area, the cancer cells alone, then the toxicity associated with chemotherapy may be avoided and, most importantly, higher drug concentrations may be achieved at the tumour site. Prodrug activation has been used in gene therapy trials in the USA in patients with brain tumours.

1.8 In this study in breast cancer patients, the prodrug is the compound, 5-fluorocytosine (5-FC). 5-FC is a relatively non-toxic compound used to treat fungal infections. 5-FC can be converted by the bacterial *enzyme, cytosine deaminase*, to a more toxic drug, 5-fluorouracil (5-FU). 5-FU is cytotoxic and is effective clinically against some human malignancies including breast, pancreatic and gastric cancers.

*Because it has been necessary to use some technical terms in describing the protocols, a glossary is appended to describe these. Words appearing in the glossary are italicised the first time they appear in the text.

1.9 The genetic prodrug activation therapy system in this trial uses a gene delivery system comprising the gene *encoding* for the enzyme cytosine deaminase (capable of the 5-FC → 5-FU conversion) and a control element of the cancer gene ERBB2 (see Paragraph 1.10). The ERBB2 gene is frequently *overexpressed* in many tumour types including breast carcinoma. Although both normal cells and cancer cells may be *transfected* by the gene delivery system, the enzyme gene will only be "switched on" in cancer cells because of their high levels of ERBB2 *expression*.

1.10 The gene delivery system used in this study is a *plasmid* DNA (p-ERCY) containing the cytosine deaminase gene to be controlled by the ERBB2 *promoter*. The aim of the study is to inhibit selectively the growth of metastatic skin nodules in patients with breast cancer by the direct injection of plasmid DNA and the systemic administration of the non toxic prodrug (5-FC). A total of 10 post menopausal women will be recruited into this phase I study.

1.11 In August 1995 GTAC gave conditional approval to this study, subject to minor changes to the clinical protocol and a simplification of the patient information sheet.

CANCER OF THE CERVIX

1.12 Cancer of the cervix has a worldwide incidence of 500,000 new cases each year. This form of cancer accounts for about 7% of all cancers of the uterus.

1.13 The group of human viruses known as papillomaviruses is associated with the induction of a range of benign *proliferative diseases* including warts and laryngeal papillomas. Some of these may progress to become malignant.

1.14 Papillomavirus DNA is often found in biopsies from patients presenting with cancer of the cervix and an association between the virus and such cancers has been proposed.

Use of a recombinant vaccinia virus for therapy of cervical cancer - University Medical School of Wales

1.15 This study aims to investigate whether a vaccinia virus modified to encode *papillomavirus* proteins can elicit a specific immune response in patients with cancer of the cervix. The proposers initially sought GTAC's opinion on whether such a trial fell within the Committee's definition of gene therapy. GTAC advised that the use of a recombinant virus in these patients raised sufficient questions as to justify committee scrutiny (see section 3).

1.16 The protocol sought to revaccinate up to five patients diagnosed as having invasive carcinoma of the cervix with a single *percutaneous* dose of the genetically modified *vaccinia virus* which had been designed to induce the production of *cytotoxic T cells* with the capacity to recognise papillomaviral proteins on tumour cells and to destroy such cells.

1.17 The proposal was reviewed at the May 1995 meeting and was approved subject to amendments to the patient information sheet.

HURLER'S SYNDROME

1.18 Hurler's syndrome is one of a group of rare inherited errors of metabolism which affect complex molecules called mucopolysaccharides. In the severe form of the disorder the genes coding for the enzyme alpha-L-iduronidase (IDUA) are defective or missing. Between one in 50,000 and one in 100,000 live births are affected so that in England and Wales about 10 children a year may be born with the condition.

1.19 The disorder usually shows itself clinically during the first year of life and is progressive. Mental development is slowed, bony abnormalities affect the face, limbs and heart and lung problems lead ultimately to death, usually in the child's first decade.

1.20 Treatment of severe Hurler's syndrome is very limited. The only proven effective approach is to carry out bone marrow transplantation before the age of 18 months from a matched and unaffected sibling. However, less than 1 in 4 of patients have a potential donor sibling and the use of a matched unrelated donor carries a much higher risk of death. It has been proposed, in the future, that gene therapy may prove helpful for some children.

A study of the efficacy of transplantation of autologous retroviral transduced bone marrow in patients homozygous for the W402X mutation (Hurler's syndrome) - University of Manchester and the Royal Manchester Childrens Hospital.

1.21 In this protocol the proposers intend to use *autologous* bone marrow (the patient's own marrow), in which the cells have been genetically modified with a *retrovirus* vector, pLX, to express the IDUA gene.

1.22 Children under the age of 18 months with the W402X mutation reponsible for the most severe form of the disease and who do not have a matched sibling may be eligible for the trial. Bone marrow will be taken; one half being kept as a "back up" and the remaining transduced with the pLX vector. The modified marrow will then be returned to the patient after treatment with cyclophosphamide (a bone marrow suppressive drug) as *sub-ablative conditioning* chemotherapy.

1.23 Initially, 3 patients will be recruited, with further recruitment of eligible patients if persistent IDUA expression is seen.

1.24 GTAC met to review this protocol in December 1995 and approved the trial, subject to the provision of supporting data relating to US trials of matched unrelated donor bone marrow transplantations and minor modifications to both the methods of evaluating IDUA levels and the patient information sheet.

PROTOCOLS STILL UNDER REVIEW AT THE END OF 1995

1.24 A further proposed programme of gene therapy research was submitted for GTAC review during the Committee's second year of work. The disease target of this protocol is head and neck cancer. This has been reviewed and a decision deferred pending the supply of additional information.

1.25 A protocol discussed by GTAC during 1994 dealing with acute myeloid leukaemia is still awaiting resubmission to the committee.

GENERAL COMMENTS ON THE PROTOCOLS

1.26 The proposals have covered quite a range of different areas of clinical science from those reviewed in 1994 and have raised new questions and new problems. All the proposers are to be complemented on the way in which they have responded to the requests for the additional information needed by the Committee to complete its review in each case.

1.27 The Committee is grateful to proposers for their patience in answering the wide range of questions put by members when the protocols were reviewed at its meetings.

1.28 GTAC will continue the practice of seeking advice as appropriate from its panel of expert advisers prior to consideration of protocols and will widen the panel membership as necessary. The Committee wishes to record its thanks to the panel for their invaluable contribution to its work.

1.29 In the first Annual Report, the Committee indicated that a submission to GTAC should be made at least 90 days before the anticipated date of review by the Committee. During 1995 GTAC has met the target of reviewing proposals within that 90 day period whenever a completed protocol has been made available.

1.30 Dates for GTAC meetings during 1996 are:

22 February
16 May
24 July
2 October
18 December

SECTION 2 - PROGRESS REPORT ON GENE THERAPY RESEARCH PROTOCOLS APPROVED BY GTAC

2.1 Of the ten gene therapy research protocols approved by GTAC or by its predecessor, the Clothier Committee, (up to December 1994), nine gene transfer studies have been carried out. GTAC's first annual report contained a brief review of the first two UK trials (a single patient with severe combined immune deficiency, and the delivery of the human cystic fibrosis gene to the nasal epithelium of 9 patients).

2.2 By the end of 1995 the number of patients recruited into gene therapy research trials had risen to 55 in 9 studies (see Annex 4).

2.3 No adverse reactions have been reported to date and GTAC hopes to receive detailed reports on all these trials during 1996.

2.4 Of the remaining four studies for which GTAC has given outline approval, restructurisation, availability of reagents and protocol modifications are among some of the reasons delaying the start of clinical trials.

SECTION 3 - GENE THERAPY : REGULATORY ISSUES

3.1 In its first guidance note issued in 1994[3], GTAC attempted to provide a useful definition of what type of work should be considered to be covered by the term "gene therapy". In the early stages of development of clinical research involving gene transfer, the Committee felt that it would be important to use a broad definition so as to cover novel methods as they were introduced.

3.2 During 1994 GTAC received some inquiries seeking an interpretation of the guidance note. Paragraph 13 of the GTAC Guidance states:

> "It is not possible, at this time, to produce a list of research techniques that lie within the scope of GTAC review. Somatic gene therapy research is considered to include the use of genetically modified organisms and/or modified nucleic acids to modify human somatic cells for potential therapy or for other research purposes in human subjects. Studies in which the aim is to induce or enhance an immune response to a vector encoded microbial immunogen are considered not to be covered by this definition of somatic gene therapy. Investigators who are unsure about the status of their research should seek advice from GTAC through the Secretariat".

3.3 The "exemption" described in Paragraph 3.2 was intended to help differentiate trials in which plasmid or other vector DNA is introduced for the purpose of therapy (such as that from the Royal Postgraduate Medical School, Paragraph 1.7 - Breast Cancer) from attempts simply to raise a antimicrobial immune response by using a novel DNA based vaccine (for example against influenza).

3.4 The view of GTAC was that, whilst the present definition may include trials outside gene therapy in the strict sense, it was important to continue to examine studies that fell into a "grey area". The Committee will continue to keep this issue under review.

SECTION 4 - INTERNATIONAL DEVELOPMENTS

4.1 The first protocol for a gene therapy experiment on human subjects was approved by the Recombinant DNA Advisory Committee (RAC) of the US National Institutes of Health in March 1988. By October 1995 a total of 125 protocols had been approved in the USA, 36 of these gaining approval in the previous twelve months. Malignant diseases remain the target in approximately 70% of all the US protocols, with inherited single gene disorders and HIV trials accounting for the remainder[4]. It should be noted, however, that only about half the approved protocols had started, recruiting a total of 597 patients. The reasons for this are complex and include problems in recruiting eligible patients, delays in obtaining Food and Drugs Administration (FDA) approval and difficulties in the production/manufacture of reagents.

4.2 In the treatment of cancer by gene therapy there has been five main approaches. These are:

(i) insertion of *cytokine* genes into cancer cells ex-vivo

(ii) insertion of an HLA gene

(iii) insertion of a *"suicide gene"* into cancer cells in situ

(iv) use of *tumour suppressor genes* or *anti-oncogenes*

(v) use of the *multi-resistance* (MDR) *gene*

4.3 As well as clinical trials in the US and UK, at least twelve gene therapy protocols have commenced in other countries, including Italy, France, Germany, Netherlands, Poland and China[5].

SECTION 5 - OTHER GTAC ACTIVITIES - GUIDANCE NOTES

WRITING INFORMATION LEAFLETS FOR PATIENTS PARTICIPATING IN GENE THERAPY RESEARCH.

5.1 In 1995 GTAC published a booklet which provides detailed advice for principal investigators and clinicians on writing information leaflets to patients participating in gene therapy research[2]. Particular attention is paid to the presentation and provision of written material for patients, their families and friends. The general principles of writing a patient information leaflet are summarised in the document. Guidance is given on the various criteria of its formulation and evaluation. The use of such leaflets should be part of a comprehensive programme for providing information which should of course include face to face discussion with the clinician.

SECTION 6 - REFERENCES

1 **Gene Therapy Advisory Committee:** First Annual Report November 1993-December 1994. Health Departments of the United Kingdom. London, Department of Health. March 1995.

2 **Gene Therapy Advisory Committee**: Writing Information Leaflets for Patients Participating in Gene Therapy Research. London, Department of Health. August 1995.

3 **Gene Therapy Advisory Committee**: Guidance on Making Proposals to Conduct Gene Therapy Research on Human Subjects London. Department of Health. September 1994.

4 **French-Anderson, W**: (Editorial) End-of-the-year Potpourri. Human Gene Therapy 1995. 6: 1505-1506.

5 "Human Gene Marker/Therapy Clinical Protocols". Human Gene Therapy. 1995 6: 1659-1678.

SECTION 7 - GLOSSARY

ADA deficiency

In many inherited genetic diseases, a gene is missing. The lack of the gene product, in this case the enzyme adenosine deaminase, can cause cells to function incorrectly and die.

Anti-oncogenes

Genes whose protein product inhibits the function of cancer genes.

Autologous

Describes a type of "self" transplant which uses organs, tissues or cells which originated from the recipient (receiving) patient or host organism.

B cell

A type of white blood cell, important in immunity.

ß galactosidase (ß-gal)

An enzyme found in the common gut bacterium, E coli which is used as a label for showing that a gene has been successfully transferred into a new cell.

Body cell (somatic cell)

Any cell of the body except a germ line cell. Changes in body cells, notably changes in their genetic make-up, affect only the individual who possesses them, not individuals of succeeding generations.

Bone marrow transplantation

Bone marrow describes the soft tissue found in the cavities of bone. Bone marrow transplantation is the transfer of blood cells found within these cavities to a recipient (receiving) patient.

Cationic liposome (see liposome)

Cell (see also: B cell, body cell, germ line cell, somatic cell)

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

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)

The protein plays an important role in controlling the passage of salts out of cells. In cystic fibrosis the gene controlling this protein (the CFTR gene) is faulty.

Cytokine genes

Genes whose protein products help control white blood cell behaviour.

Cytokines

Proteins which help control the behaviour of white blood cells.

Cytosine deaminase

An enzyme involved in the elimination of toxic (nitrogen) waste from the body.

Cytotoxic T cells

A sub group of white blood cells implicated in the destruction of "non self" (foreign) cells.

DNA (deoxyribonucleic acid)

The chemical substance of which a gene is made and which encodes genetic information.

Encoding

Refers to sections of DNA which contain sufficient genetic information to produce a protein product when expressed.

Enzyme

A protein which catalyses one of the body's many chemical reactions, which together constitute metabolism - the processes that enable continued functioning and growth. A deficit in the production of an enzyme or its working may result in an inherited disorder of metabolism.

Express (see gene expression)

Gene

A sequence of DNA which codes for one protein and which may be responsible for an inherited character difference.

Gene expression

The production by a cell of the protein for which the specific gene codes.

Gene therapy

Used without qualification means the genetic modification of body cells of an individual patient, directed to alleviating disease in that patient.

Genetic disease or disorder

Afflictions which are the result of defects in the genetic endowment 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 from the interaction of multiple genes and external factors in fetal development. Later in life such interactions seem to be the basis of many of the common serious disorders, such as heart disease, diabetes, and cancer, although these are not usually thought of as genetic disorders.

HLA (Human-Leucocyte-Associated) Antigen

In humans, these proteins were first described on the surface of white blood cells (leucocytes). HLA antigens are important in the body's recognitions between "self", as opposed to "non self" organs, tissues and cells.

Homozygous

Describe the degree of similarity of the genetic information, between the pair of genes an individual inherits from parents. An individual is homozygous if the inherited information is the same.

Immunoglobulin

A protein which has antibody activity.

Liposome

A fatty droplet which can cross into a cell carrying the genes needed for gene therapy.

Lymphocyte

A type of white blood cell, important in immunity.

Metabolism

Describes the series of chemical reactions taking place within the body. These reactions are necessary for its maintenance and growth.

Metastatic, metastases

Disease, usually cancer, that has spread from one site to another unconnected organ.

Molecular biology

The study of proteins and nucleic acids, substances that make up the living world, their structures and their relationship to biochemical activity; and the substances that are the repositories of genetic information and the agencies for its communication from one generation to the next.

Multi resistance (MDR) gene

Genes whose protein product incapacitate the toxic effect of certain types of drugs. MDR is a associated with cancerous mutations to the cell.

Mutation

A molecular event in which DNA is altered with genetic consequences. A gene which has undergone mutation is called a mutant; so also is an organism in which the mutant gene is expressed.

Nucleic acid

DNA is a type of nucleic acid. A more specialised type of nucleic acid is called RNA which is the genetic material of some viruses such as retroviruses.

Oncogene

A gene whose protein product is implicated in the production of cancer cells.

Palliative Treatment

Treatment whose principal aim is to lessen the discomfort the patient may experience during illness.

Papillomavirus

In humans, this virus is implicated as a major causative element in the production of some cancerous and non cancerous (benign) tumours.

Percutaneous

Describes the process of penetration through the skin.

Plasmid

A small piece of DNA, usually of bacterial origin, capable of reproducing in human cells and carrying genes. Plasmids are used in some gene therapy trials in place of viral vectors or liposomes.

Proliferative diseases

Illness caused by the unregulated multiplication of cells within the body.

Promoter

A short piece of DNA which controls other genes. Changing the promoter may alter the behaviour of genes.

Protein

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

Recombinant DNA

Using modern scientific techniques it is possible to make alterations to DNA in the laboratory. Genes can be removed, relocated or added, changing the sequence of genes. Such modified DNA is called recombinant.

Retrovirus

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 safe so that they can enter a human cell carrying a gene for gene therapy without causing disease.

Somatic cell (see body cell)

Sub-ablative conditioning

Describes the preparative treatment of a transplant patient. Sub-ablative treatment aims to partially suppress the patient's immune response to the transplanted organs, tissue or cells.

Suicide genes

In the presence of certain drugs, the protein products of these genes will cause the destruction of the cell carrying the expressed suicide gene.

Systemic

Describes events taking place within the circulatory networks of the body. The blood circulatory network is one of the most important.

Transfection, Transfected

Describes the entry and expression into a cell of the gene product carried by the vector.

Tumour suppressor genes

The protein product of the gene regulating the multiplication of cells. Their absence or dysfunction is associated with the production of cancer cells.

Vaccinia virus

This is a vaccine strain of virus. Live vaccinia virus has been used extensively in smallpox eradication programmes.

Vectors

In most situations, a new gene cannot be added to human cells without being transported into the cell in some form of a carrier - usually a virus, a liposome or a plasmid.

Virus

A tiny infectious organism, too small to reproduce outside a host cell. Viruses carry nucleic acid surrounded by protein. Some cause disease, eg chicken pox, influenza. Some viruses however, suitably modified, can be used in research as a means of delivering a gene into cells.

ANNEX 1 - TERMS OF REFERENCE OF GTAC

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 fr 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 fr 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

- sound information, counselling and advice to be given to the subject (or those acting on behalf of the subject)

- the outcomes of therapy to be assessable;

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

ANNEX 2 - MEMBERSHIP OF GTAC

Chairman

Professor Dame June Lloyd, DBE MD FRCP
formerly Professor of Child Health
Institute of Child Health, London

Members

Dr Elizabeth Anionwu, PhD, RGN, HV Tutor
Senior Lecturer in Community Genetic Counselling
Mothercare Unit of Clinical Genetics and Fetal Medicine
Institute of Child Health, London

Mrs Rosemary Barnes
Director, "Wellbeing" – The health research charity for women and babies, London

Professor Martin Bobrow, CBE DSc, MB, BCh, FRCP, FRCPath*
Cambridge University
Department of Medical Genetics
Clinical Genetics Unit, Cambridge

Professor Derek Crowther, PhD, MB, BChir, MA, MSc, FRCP, FRCR
Christie CRC Research Centre
CRC Department of Medical Oncology
University of Manchester

Professor Anthony Dayan, MD, FRCP, FRCPath, FFPM, FIBiol
Director
Department of Toxicology
St Bartholomew's Hospital, London

The Rev. Canon Dr Keith Denison, MA, PhD.
The Church in Wales
Diocese of Monmouth

Dr Brenda Gibson, FRCP, FRCPath, DFM
Department of Haematology
Royal Hospital for Sick Children, Glasgow

Mrs Rosemary M Knights, RGN, OND, DN †
Chief Executive
Warrington NHS Trust Hospital, Cheshire

Professor Peter Lachmann, FRCP, FRCPath, FRS
Molecular Immunopathology Unit
Medical Research Council, Cambridge

Dr Theresa Marteau, MSc, PhD, CPsychol
Psychology and Genetics Research Group
United Medical and Dental School, London

Professor Norman Nevin, BSc, MD, FRCP, FRCPath
Northern Ireland Genetics Services
Department of Medical Genetics
The Queen's University, Belfast

Miss Eleanor F Platt QC
The Temple, London

Dr Brian Richards, CBE, BSc, PhD
Executive Chairman,
Peptide Therapeutics Group PLC,
Cambridge

Mr Nick Ross*
Broadcaster and journalist

Professor C Michael Steel, MB, ChB, PhD, DSc, FRCPEd, MRCPath
School of Biological and Medical Sciences,
University of St Andrews, Fife.

Professor Robin Weiss, PhD, FRCPath, Hon. MRCP*
Institute of Cancer Research
Chester Beatty Laboratories, London

Observers

Dr John Modle
Department of Health, London

Dr Brian Davis MRCP
Medicines Control Agency, London

Dr Lincoln Tsang
Medicines Control Agency, London

Secretariat

Mr Anthony J Taylor MSc, MIOSH
Dr Veronica Lecomte
Mrs Margaret Straughan

**** Members retiring in 1995.***
† Member resigned in 1996.

ANNEX 3 - EXPERT ADVISERS TO GTAC

During the period of this second report, GTAC sought the views of the following expert advisers during the review of protocols submitted to the Committee.

Professor Alan Craft, Royal Victoria Infirmary, Newcastle Upon Tyne

Professor Kay Davies, University of Oxford

Professor John Dodge, Queen's University of Belfast

Professor James Neil, University of Glasgow Veterinary School

Professor Robert Souhami, Middlesex Hospital, London

Dr John Arrand, Paterson Institute for Cancer Research, Manchester

Dr Mary Collins, Chester Beatty Laboratories, London

Dr Nicholas Jones, ICRF Laboratories, London

ANNEX 4 - GENE THERAPY RESEARCH (1993/95)

#	Details	Centre	Outline Approval	Trial Commenced	Final Report back	Vector/gene	Packaging cell line	No. of Patients
001	SCID-ADA	Institute of Child Health/ Great Ormond Street Hosp	1-93	3-93	11-93	ADA	ψCRIP/GP+ env AM12	1
002	CF Nasal trial	Royal Brompton Hosp	3-93	9-93	6-94/ 1-96	Liposome DC-Chol/CFTR	–	15
003	B-cell lymphoma	MRC Cambridge	7-93	11-94	–	pVAC1/anti idiotype immunoglobulin	–	3
004	Neuroblastoma	ICRF Bristol	2-94	–	–	LNL-6/neo G1N-neo	PA317	–
005	Metastatic melanoma	ICRF Oxford	5-94	6-95	–	pNASSB-IL2 pNASSB-BGal	–	5
006	Metastatic melanoma MFG-S-IL2	Institute of Cancer Research/ Royal Marsden Hosp	2-94	10-94	–	MFG-S-IL2	GP+env AM12	5
007	CF Nasal trial	Oxford/Cambridge	2-94	5-95	1-96	Liposome DC-Chol/CFTR	–	12
008	CF Nasal trial	Edinburgh	5-94	6-95	–	Liposome DOTAP-CFTR	–	12
009	CF lung trial	Royal Brompton Hosp	9-94	–	–	Liposome DC-Chol/CFTR	–	–
010	Lymphoma	University College London Medical School	12-94	10-95	–	pHaMDR-1	AM12M1	1
011	Breast Cancer	Hamersmith Hospital	10-95	–	–	pERCY	–	–
012	Cervical Carcinoma	University of Wales, Cardiff	6-95	9-95	–	TA-HPV	CR2C9	1
013	Hurler's Syndrome	Royal Manchester Children's Hospital Manchester	12-95	–	–	pLX	GP+env AM12	–

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