Report on the potential use of gene therapy in utero / Gene Therapy Advisory Committee.

GENE THERAPY
ADVISORY COMMITTEE

REPORT ON THE POTENTIAL USE OF GENE THERAPY *IN UTERO*

Health Departments of the United Kingdom
November 1998

GENE THERAPY ADVISORY COMMITTEE

REPORT ON THE POTENTIAL USE OF GENE THERAPY *IN UTERO*

Health Departments of the United Kingdom
November 1998

The GTAC Secretariat may be contacted at:

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

Tel:0171-972 4017
Fax:0171-972 4196

E Mail: mstraugh@doh.gov.uk

CONTENTS

THE POTENTIAL USE OF GENE THERAPY *IN UTERO:* A REPORT BY THE GENE THERAPY ADVISORY COMMITTEE

BACKGROUND

1. Since gene therapy was first attempted in1989, there have been over 300 clinical protocols approved world wide. 30 research trials in patients have been considered in the UK by the Gene Therapy Advisory Committee (GTAC) established in 1993 to review such work[1].

2. There is a wide consensus that, at present, gene therapy should be restricted to attempts to modify somatic (body) cells so that changes will not be passed to successive generations. GTAC has confirmed that its view remains that gene modification of the germ line, where effects could be transmitted to offspring, should not yet be attempted.

3. To date, all but two of the trials of somatic gene therapy considered by GTAC have been intended to be performed in adults or young persons over 16 years. The two exceptions were in young children born with inherited single gene disorders, Hurlers Disease and Severe Combined Immuno-Deficiency (SCID), where it may be possible to correct the gene deficiency before serious or life threatening symptoms develop.

4. However in many genetic disorders it may not be possible to use such potential therapies after birth. In some disorders the damage is already done before birth and there may be good clinical reasons to intervene *in utero* to try and correct the genetic damage.

5. Interventions *in utero* are not new. Surgical procedures are used to correct the accumulation of fluid in the bladder or chest; steroid drugs can be infused into the developing fetus and transfusion of blood or platelets directly into the fetus are established procedures.

STEM CELL TRANSPLANTATION

6. To the list above, we must now add stem cell transplantation. There is considerable scientific and clinical interest in pluripotent haematopoietic stem cells (PHSC) - those cells that can self renew and which produce all lineages of blood cell formation. The potential to use PHSC before birth to treat congenital disease in theory offers a number of possible advantages.

   (i) Because the fetal immune system has not yet developed, it will not reject foreign cells. Unlike bone marrow transplantation post-birth there is no need to match donor cells.

   (ii) The fetus will become "tolerant" to the foreign cells allowing for further treatment after birth, again without the risk of rejection.

   (iii) Intervention *in utero* will permit "correction" of a disorder before clinical manifestations have developed.

7. There is already a considerable body of evidence, from animal models and from a small number of *in utero* transplantations of unmodified bone marrow progenitor cells in human fetuses, that there is a "window of opportunity" that technically permits and favours engraftment of transplanted PHSC *in utero.*

8. There have already been a small number of such trials during human pregnancies involving such disorders as X-linked SCID, α-thalassaemia, sickle cell anaemia and β-thalassaemia.

9. Possible sources of human PHSC include cord blood, fetal liver, adult bone marrow and adult peripheral blood. The use of cells derived from another fetus raises both practical and ethical issues, and to date much work has concentrated upon the use of adult derived cells as a renewable, low risk and ethically acceptable source of PHSC.

10. The technical aspects of *in utero* cell transplantation may be less complex than one might at first imagine. The fetal circulation can be accessed transabdominally under ultrasound from 17 weeks gestation. This technique is well established, in standard practice and the risks associated with it are well documented. The experimental technique of coelocentesis which accesses the exolcoelomic cavity by transvaginal puncture, may offer the possibility of stem cell engraftment much earlier in gestation (10+ weeks). Such very early interventions do not raise the issue of fetal awareness and pain. (The Royal College of Obstetricians and Gynaecologists Working Party Report on Fetal

Awareness, October 1997 [2], concluded that it is not possible for the fetus to be aware of events before 26 weeks' gestation).

THE POTENTIAL USE OF GENE THERAPY IN UTERO

11. A second approach will build on the PHSC trials described above and will apply genetically modified cells *in utero* - ie *in utero* gene therapy. It has been argued that two key issues need to be addressed before such an intervention is considered;

    (i) that there must be a clear advantage over post-natal gene therapy;

    (ii) that there must be an advantage over therapy with unmodified cells.

12. Pre-natal gene therapy has been proposed as most appropriate in disorders which result in irreversible illness or death in the pre or neonatal period. Examples may include Type 2 Gaucher's Disease, Krabbe's disease, Hurler's Disease etc. Considerable interest in the possibilities of gene therapy *in utero* was also stimulated by a letter to the "Lancet" in March 1997 in which an adenovirus vector was used *in utero* to correct the cystic fibrosis phenotype in mice [3].

ACTION BY GTAC

13. At its September 1997 meeting GTAC agreed to establish a subgroup on New and Emerging Technologies (NETS).

14. The remit of the subgroup is to aid GTAC to fulfil one of its terms of reference "to advise UK Health Ministers on developments in gene therapy research and their implications". The subgroup's function was to report to GTAC on areas of any new technology that may have implications for gene therapy research or techniques.

15. The subgroup was asked to look at the potential of gene therapy *in utero*. Members were provided with the Minutes of the December 1994 meeting of the US Recombinant DNA Advisory Committee (RAC), which discussed this subject and a review based upon papers and posters presented at the "Second International meeting on *in utero* stem cell transplantation and gene therapy" held in September 1997 in Nottingham.

16. NETS met to consider this subject in November 1997 and presented its report to GTAC in February 1998.

NETS REPORT ON IN UTERO GENE THERAPY

17. In considering the principles that should apply to *in utero* gene therapy, NETS first revisited and reaffirmed the six key elements currently employed by GTAC when considering gene therapy for adults and children. These were developed by GTAC upon the recommendations of the Clothier Committee Report of 1992[4]. NETS concluded that these principles should also apply to *in utero* gene therapy.

18. These six principles state that;

    (a) gene therapy is research and not innovative treatment;

    (b) only somatic therapy should be considered;

    (c) in view of safety and ethical difficulties germ line interventions are off limits at present;

    (d) gene therapy should be restricted to life threatening disorders where no current alternative effective treatments are available;

    (e) patients should take part in gene therapy research trials only after a full explanation of the procedures, risks and benefits and after they have given their informed consent, if they are capable of doing so; and

    (f) recognising that some people, including young children, may not be able to give such consent, therapeutic research involving such patients must not put them at disproportionate risk.

19. The subgroup kept these principles in mind as they discussed *in utero* therapy issues, considered the papers prepared by RAC and heard presentations from relevant experts. The subgroup considered some of the key issues raised by both stem cell transplantation (SCT) using PHSC and gene therapy interventions *in utero*. The group considered both the scientific validity and the potential treatment advantages of such therapies.

20. The group considered that SCT *in utero* offered therapeutic opportunities for a wide range of genetic disorders, and that such techniques were much more likely to be used in the short term than *in utero* gene therapy.

21. Fetal liver cells were identified as the transplant of choice with discrete scientific advantages over either cord blood or cells derived from adults. The subgroup noted that SCT with fetal liver cells is not a "new" technique having been first attempted in the UK over thirty years ago.

22. The subgroup agreed that there are ethical issues involved in the use of fetal tissues - those identified in the Polkinghorne Report "Review of the Guidance on the Research Use of Fetuses and Fetal Material"[5]. The NETS subgroup endorsed the code of practice recommended by the Polkinghorne Committee. Particular consideration should be given to those who might decline the use of fetal tissue whilst consenting to SCT using other donor tissue.

23. In considering in utero gene therapy the subgroup agreed that it was unlikely to be feasible in the short term. Reasons included the lack of a strong list of candidate disorders for potential therapy, and that at this stage, SCT offered better prospects for success.

24. The subgroup concurred with RAC's concern that *in utero* gene therapy may give rise to germ line effects. It was noted that in a sheep model it had been possible to transmit a gene insert *in utero* into multiple organs and tissues and to have the foreign gene(s) pass to subsequent generations.

25. The subgroup considered that there were particular concerns about the risk of germ line involvement in the use of a direct, or vector, mediated gene therapy *in vivo*. Such interventions are unacceptable in view of the safety and ethical difficulties that remain at present.

26. In contrast, the subgroup considered that the use of genetically modified stem cells in SCT was a possibility. Such *ex vivo* modification would be unlikely to carry with it any higher risk to the germ line than the trials of post natal somatic gene therapy which have already been approved. They agreed that *ex vivo* genetic modification prior to *in utero* SCT does not raise any new ethical concerns and could be considered by GTAC in the same manner as somatic gene therapy.

CONCLUSIONS

27. Following their discussion, the subgroup concluded that:

    (a) they did not consider that there were any new ethical issues raised by *in utero* gene therapy that were not already recognised in other interventions *in utero*, or in the use of gene therapy in other situations. The issue of consent remains a matter solely for the pregnant woman.

    (b) In order to be ethical, the risks of the physical procedures would need to be known.

    (c) The disorder or disease treated would need to be life threatening, or associated with severe disability, and for which no suitable treatment is available after birth, in order to justify intervention *in utero*.

    (d) Existing concerns with regard to gene therapy, in particular regarding the potential for germ line transmission, remain. Such concerns would need to be fully answered in the event of any protocols proposing *in utero* gene therapy being presented to GTAC.

(e) With this in mind, GTAC believes that the use of a direct, or vector, mediated gene therapy *in utero* are unlikely to be acceptable for the foreseeable future, in view of the safety and ethical difficulties.

(f) Somatic gene therapy protocols which involve *ex vivo* genetic modification of stem cells prior to bone marrow transplantation in infants have already received approval from GTAC. The Committee believes that stem cell transplantation *in utero* would be unlikely to carry with it significantly higher risk to the germ line than such post natal somatic gene therapy.

(g) Such interventions could be considered by GTAC in the same manner as somatic gene therapy, ie subject to the strict criteria already established by the Committee.

November 1998

REFERENCES

[1] Department of Health. GTAC Fourth Annual Report.

[2] The Royal College of Obstetricians and Gynaecologists. *Fetal Awareness. Report of a Working Party (October 1997).* Published by the RCOG Press. ISBN 1 900364 07 7.

[3] Larsen JE et al (1997). *Reversal of cystic fibrosis phenotype in mice by gene therapy in utero.* The Lancet 349 (9052). p619.

[4] Department of Health. *Report of the Committee on the Ethics of Gene Therapy.* London HMSO, 1992; Cm 1788.

[5] *Review of the Guidance on the Research Use of Fetuses and Fetal Material.* (July 1989). Published by Her Majesty's Stationary Office. ISBN 0 10 107622 3.

GLOSSARY

Genes

The biological units of heredity.

Gene therapy

The genetic modification of body cells of an individual patient, directed to alleviating disease in that patient.

Germ-line

The cells which transmit genetic information to the next generation. They are the sperm in males and the egg cells in females.

In utero

In the womb.

Peripheral blood

Blood circulating around the body in veins and arteries.

Stem cells

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

Somatic cells

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

ANNEX A

GTAC Members of the New and Emerging Technologies (NETS) group.

Canon Keith Denison (Chairman).

Mrs Rosemary Barnes

Dr Brenda Gibson

Mrs Ann Hunt

Mrs Irene Train

Professor Ian Hart

Professor Michael Steel

Co-opted individuals taking part in discussion of *in utero* gene therapy in November 1997.

Dr Colin Casimir
Department of Haematology
St Mary's Hospital Medical School, London.

Dr David Liu
Department of Obstetrics and Gynaecology
City Hospital, Nottingham.

ANNEX B - GTAC MEMBERS

Chairman

Professor Norman C Nevin BSc MD FFPHM FRCPath FRCP Ed FRCP

Members

Professor Elizabeth Anionwu PhD RGN HV

Mrs Rosemary Barnes

Professor John Burn MD FRCP

Professor Anthony Dayan MD FRCP FRCPath FFPM FIBiol

Reverend Dr Keith Denison MA PhD

Dr Brenda Gibson FRCP FRCPath DFM

Professor Ian Hart BVSC MRCVS PhD FRCPath

Mrs Ann Hunt

Professor Patrick Johnston MRCI MB BCh BAO

Professor Theresa Marteau MSc PhD CPsychol

Professor James Neil BSc PhD FRSE

Professor Anthony Pinching DPhil FRCP

Miss Eleanor Platt QC

Sir Brian Richards CBE BSc PhD

Professor C Michael Steel MB ChB PhD DSc FRCP Ed MRCPath

Mrs Irene Train RGN RM RHV QIDN

Produced by Department of Health
14369 HP 1.6k Nov 98 (SWI)
CHLORINE FREE PAPER