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## Somatic gene cell therapy ethical?

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## Ethics

- Altruism
- Sense of Honour
- Justness
- Respect for others
- Solidarity
- Ability to forgive

## Bioethical principles

Medical conduct, physicians obligations

(Belmont Criteria, 1979)

- Autonomy of the patient
- Beneficience
- Non-maleficiency
- Justice
- Trust

## Occidental Ethics

Western ethical thinking, "Christian Ethics"

- Founders:
  - Socrates, Plato, Aristoteles
    - Greek philosophy: moral virtue
      - values are natural rather than conventional
      - ethics as science
  - Saint Augustinus, Thomas Aquinas
    - Incorporation of Greek ethics
    - Attainment of happiness
    - God given natural order
  - Immanuel Kant
    - Categorical imperative: the individual shall act in a way, that his action can be regarded as general law
  - Modern ethics
    - Different schools:
      - Value ethics, existentialistic ethics, American bioethics, Marxian ethics, theological ethics

## "Non Western Ethics"

partly religious fixed

- Ethical rules in Buddhism
  - end of rebirth, Nirvana
- Ethical rules in Confucianism
  - appreciation of well being of the community above the well being of the individual
- Ethical rules in Mosaic religion
- Ethical rules in Islamic religion
- Ethical rules in natural religions
  - Massai religion, African religious communities, Schamanism, etc.

## Hippocratic oath

Obligation for modern physicians

- Curative element: Main demand of a physician is to do everything for the benefit of a patient to the best of his knowledge and ability to keep away damages, injustice and risks.
- Obligation to minimize suffering of a patient
- Strict prohibition to apply lethal poison or to give advise to use deadly poison
- Any prolongation of suffering has to be prevented
- The basic obligation of a physician is to preserve life
- The decision on life and death of a patient is not up to a physician

**UNESCO Bioethics Declaration on Human Rights**
Paris, September 2005
Aims – Article 2

- Universal framework of principles and procedures to guide states in bioethics
- to guide the actions from individuals as well as communities, public and private
- to promote respect for human dignity and protect human rights
- to recognize the importance of freedom in scientific research
- to foster multidisciplinary and pluralistic dialogue
- to promote equitable access to medical, scientific and technological development
- to safeguard and promote the interest of present and future generations
- to underline the importance of biodiversity

## Physicians' Ethical Duties to Patients

- Prevent harm to patients (non-maleficence)
- Try to do good to patients (beneficence)
- Respect patients' dignity and autonomy
- Respect patients' confidentiality and privacy
- Be honest with patients
- Practice fidelity in the care of patients
- Avoid conflicts of interest in patient care and research and adequately disclose those that cannot be avoided
  - Bernat JL. *Ethical Issues in Neurology*, 2nd ed. Boston: Butterworth-Heinemann, 2002.

## Definition of Gene Therapy

„Introduction of genetic material into an individual, or the modification of the individual's genetic material, in order to achieve a therapeutic or prophylactic objective."

WHO, Genomics and World Health, World Health Organization, Geneva, 2002

- **Somatic gene therapy**
  - Somatic cells of an individual are targeted, only the individual is affected, change is not heritable
- **Germline gene therapy**
  - Germ cells (sperm, egg) are modified by the introduction of a functional gene into their DNA, change is heritable

## Aims of Gene Therapy For Neurodegenerative Diseases

- Neuroprotection
- Restoration of neuronal function
- Replacement of deficient proteins

## Gene therapy for neurological disorders Unique Challenges

- How to introduce the therapeutic gene across the blood-brain barrier
- How to target the therapeutic gene to one specific area of the brain
- Cerebrospinal fluid delivery
- Ex vivo gene therapy and cell transplantation
- Use of migratory cells

## What factors have kept gene therapy from becoming an effective treatment for a genetic disease? - I

- **Short-lived nature of gene therapy** - Before gene therapy can become a permanent cure for any condition, the therapeutic DNA introduced into target cells must remain functional and the cells containing the therapeutic DNA must be long-lasting and stable. Problems with integrating therapeutic DNA into the genome and the rapidly dividing nature of many cells prevent gene therapy from achieving any long-term benefits. Patients will have to undergo multiple rounds of gene therapy.
- **Immune response** - Anytime a foreign object is introduced into human tissues, the immune system is designed to attack the invader. The risk of stimulating the immune system in a way that reduces gene therapy effectiveness is always a potential risk. Furthermore, the immune system's enhanced response to invaders, which it has seen before, makes it difficult for gene therapy to be repeated in patients.

## What factors have kept gene therapy from becoming an effective treatment for genetic disease? - II

- **Problems with viral vectors** - Viruses, while the carrier of choice in most gene therapy studies, present a variety of potential problems to the patient – toxicity, immune and inflammatory responses, and gene control and targeting issues. In addition, there is always the fear that the viral vector, once inside the patient, may recover its ability to cause disease.
- **Multigene disorders** - Conditions or disorders that arise from mutations in a single gene are the best candidates for gene therapy. Unfortunately, some of the most commonly occurring disorders, such as heart disease, high blood pressure, Alzheimer's disease, arthritis, and diabetes, are caused by the combined effects of variations in many genes. Multigene or multifactorial disorders such as these would be especially difficult to treat effectively using gene therapy.

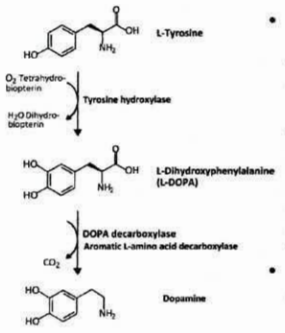
## Dopamine Gene Therapy for Parkinson's Disease in a Nonhuman Primate Without Associated Dyskinesia

(Science Trans. Med. 1, 1–10, Oct 2009)

- Parkinson patients show reduced levels of dopamine.
- The standard treatment for Parkinson is administration of pharmacological agents that transiently increase concentrations of brain dopamine (f.e. DOPA) and thereby discontinuously modulate neuronal activity in the striatum, the primary target of dopaminergic neurons. The resulting intermittent dopamine alleviates parkinsonian symptoms but is also thought to cause abnormal involuntary movements, called dyskinesias.

## Dopamine Gene therapy for Parkinson's Disease in a nonhuman primate without associated dyskinesia

(Science Trans. Med. 1, 1–10, Oct 2009)




- In a macaque monkeys model of Parkinson disease, introduction of the three critical genes for dopamine synthesis (tyrosine hydroxylase, aromatic l-amino acid decarboxylase, and guanosine 5′-triphosphate cyclohydrolase) into the striatum safely restored extracellular concentrations of dopamine and corrected the motor deficits for 12 months without associated dyskinesias (in one monkey even for 4 years).
- Novel vector: lentivirus (infects non-dividing cells such as neurons)

## Gene therapy in neurological diseases Actual state

- Parkinson
- Batten Disease
- Chorea Huntington
- Alzheimer Disease
- Diabetic neuropathy

Positive clinical response

Experience with patients, clinical trial phase I, partly II

- Limb Girdle Muscular Dystrophy
- Adenoleukodystrophy
- Primary dystonias
- Hallervorden-Spatz-Disease
- Spinal muscle atrophy

Animal model

## Occurred unwanted complications

- Acute side effects
  - Somatic reactions by causing healthy cells
    - fever, etc.
    - Hypotonic crisis
  - Psychological reactions

## Unwanted complications possible

- Acute side effects
  - Somatic reactions by causing healthy cells
    - Fever, etc.
    - drop-in blood pressure
  - Psychological reactions
- Chronic side effects
  - Somatic reaction
    - Change in the immune system
    - Secondary induced organic reactions
    - Development of cancer
  - Sperm or eggs damage
  - Psychological changes, behavioral
  - Expectations not fulfilled

## Conflicts of Interest in Gene Therapy I

- FDA financial disclosure regulations, 1999
- American Society of Gene Therapy conflict of interest statement: April, 2000:
  - Members who are "directly responsible for patient selection, the informed consent process, and/or clinical management in a trial must not have equity, stock options, or comparable arrangements in companies sponsoring the trial."

## Conflicts of Interest in Gene Therapy II

- AAMC December, 2001: *Protecting Subjects, Preserving Trust, Promoting Progress – Policy and Guidelines for the Oversight of Individual Financial Interests in Human Subjects Research*
  - All financial interests are potentially problematic
  - Significant interest review by C.O.I. committee
  - Full, prior reporting, disclosure
  - Comprehensive, transparent institutional policies
  - Rigorous, effective, and disinterested monitoring

## Somatic Gene Cell Therapy Experiments

- Raise no important new ethical issues and therefore can be treated like any other innovative non-genetic therapy
- Widespread consensus that somatic cell gene therapy is ethically acceptable
- Valid consent of the research subject is required and the experiment must be approved by IRB
- Parents consent for their children; mothers for fetuses
- American Society of Human Genetics "litmus test" asks investigators if they or a member of their own family had a disease that might benefit from gene therapy, would they enroll their loved one in the gene therapy trial in question
  - Board of Directors of the American Society of Human Genetics. *Am J Hum Genet* 2000;67:272-273

## Gene Therapy: Enhancement I

- Somatic human gene therapies to enhance capabilities such as intelligence or height, or to treat cosmetic issues such as baldness, raise an interesting set of ethical issues
- Should powerful and potentially dangerous gene therapies be developed to address these relatively minor problems?
- Are these issues even medical problems which physicians have a professional responsibility to treat?
- Or does gene therapy for enhancement represent a dangerous example of genetic engineering and eugenics that will create problems for society in the future when the technology becomes extended in ways we now cannot fully imagine?
  - Anderson WF. *Hastings Cent Rep* 1990;20(1):21-24.

## Gene Therapy: Enhancement II

- Not qualitatively dissimilar to existing pharmaceutical therapies prescribed for baldness or hormonal therapies prescribed for short stature
- Some instances may not be as medically trivial as they first appear because of the psychological damage to patients resulting from having socially undesirable physical traits
- The risks of genetic therapy for enhancement may not exceed the risk of alternative treatments with medications or surgery
- Scientific attention to and public funds designated for the development of genetic enhancement therapies should be relegated to a lower priority than for those directed against cure or prevention of genetic disease
  - Miller HI. *Lancet* 1994;344:316-317

## Fetal Gene Therapy

- Goal: After prenatal genetic testing it may be desirable to prevent or cure the disease before it creates further damage to the fetus.
- Alternative to selective abortion.
- Thoughtful utilitarian analyses of the ethical issues involved conclude that fetal gene therapy should be studied and perfected because benefits outweigh the principal harm of the practice, namely starting down the „slippery slope" towards germ-line gene therapy.
  - Fletcher JC, Richter G. *Human Gene Ther.* 1996, 7: 1605-1614.
- In German ethical thinking after World War II (responsibility ethics "Verantwortungsethik", e.g. by Hans Jonas) even the possibility of a slippery slope would prevent studying and perfecting this technology.
- Robert Spaemann:
  „Not by total action can we maintain a world inhabitable for mankind but only by a new ethos prompting us ... to consciously accept limitations."

## Germ-Line Gene Therapy

- Might be more ethically acceptable if several additional criteria were fulfilled
  - It must be shown confidently that the inserted gene would not produce adverse effects on development
  - The inserted gene must be shown not to cause chromosomal damage to future generations
  - It will be necessary to develop the technology to confidently target specific chromosomal sites
- Our ability to know the answers to these questions is sufficiently limited that these criteria cannot be satisfied for the foreseeable future
  - Fletcher JC, Anderson WF. *Law Med Health Care* 1992;20:26-38.

## Summary on Somatic Gene Therapy

- Feasible
- Not a clinical practice so far because of side effects of vector in clinical trials
- Still in experimental stage
- No ethical issues

## Do we want to play "God"?

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
ΥΠΟΥΡΓΕΙΟ ΠΑΙΔΕΙΑΣ ΔΙΑ ΒΙΟΥ ΜΑΘΗΣΗΣ ΚΑΙ ΘΡΗΣΚΕΥΜΑΤΩΝ

# International Society for Amelioration of the Quality of Life for chronic neurological patients

## 8th International Congress on current treatment and therapeutic perspectives in Alzheimer' s disease, Parkinson's disease, Multiple Sclerosis and Epilepsy

# SCIENTIFIC PROGRAM

## Delphi, Greece, European Congress Center
## February 4-7, 2010

**Secretary: Mrs Vaya Katsamperi. 1st Department of Neurology, Aristotelian University, Thessaloniki, Greece, AHEPA Hospital. St. Kyriakidi 1, 546 36 Thessaloniki, Greece**
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**17.30-19.30 Round table on Neuroethics**

**Chairmen:F.Gerstembrand, J.Toole**

J.Toole: Hippocrates to managed care
K.von Wild: To whom we are bound by the oath of Hippocrates
F. Gerstenbrand: Somatic cell therapy, ethical?
S. Baloyannis: Gene therapy from the Orthodox viewpoint
B.Lichterman, L.Lichterman: Ethics in Neursurgery

**19.30-20.00 Cello recital by Prof. Konrad Maurer**