Karl Landsteiner Institute for Neurorehabilitation and Space Neurology

Somatic Gene Cell Therapy in Neurology and Ethical Background

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8th International Congress on current treatment and therapeutic perspectives in Alzheimer's disease, Parkinson's disease, Multiple Sclerosis and Epilepsy
February 4-7, 2010,
Delphi, Greece

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."

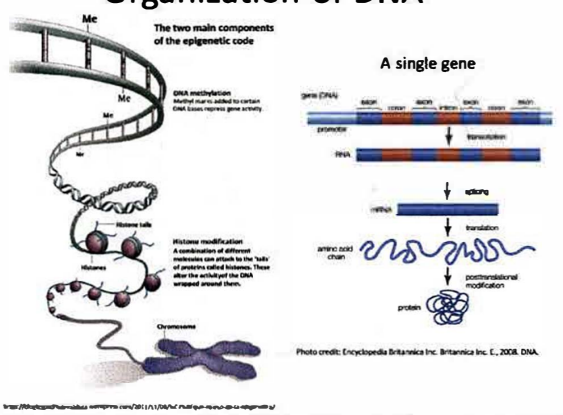
WHO, Genomics and World Health, World Health Organization, Geneva, 2002

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

Aims of Somatic Gene Therapy For Neurodegenerative Diseases

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

Organization of DNA



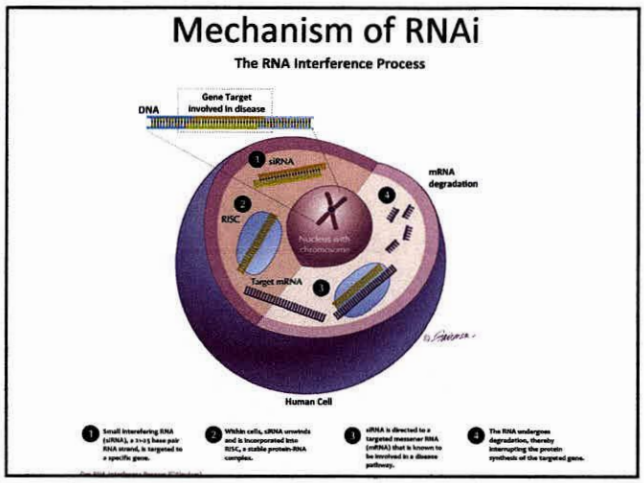
Gene therapy: principal steps

- Get a copy of the functional (wild-type) gene
- Clone it in bacteria (*E. coli*)
- Transfer cloned DNA into human cells

Categories of therapeutic strategies

- With respect to gene:
  - Replacement: Product of gene transferred into target organ replaces product of endogenous deficient gene.
  - Knockdown: Antisense oligos (artificial DNA) or siRNA (artificial RNA) inhibit expression of deficient genes.
- With respect to method of DNA delivery:
  - Isolate DNA of this gene, wrap it into liposomes and inject into human organs.
  - Transfer the gene into a virus able to infect human cells. Inject into human organs.
- With respect to target:
  - In vivo: direct introduction of genetic material into organ
  - Ex vivo: manipulation of cells in vitro followed by transplantation into organ

Mechanism of RNAi



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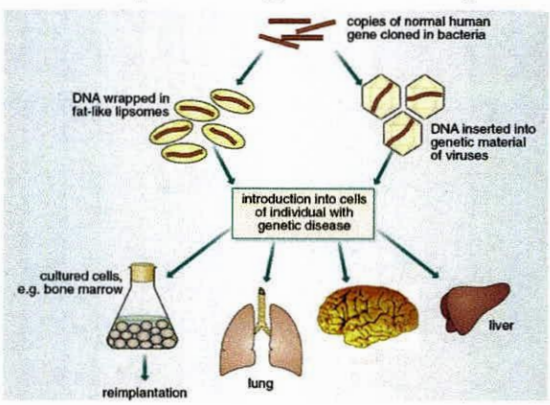
Two ways how to get DNA into organs



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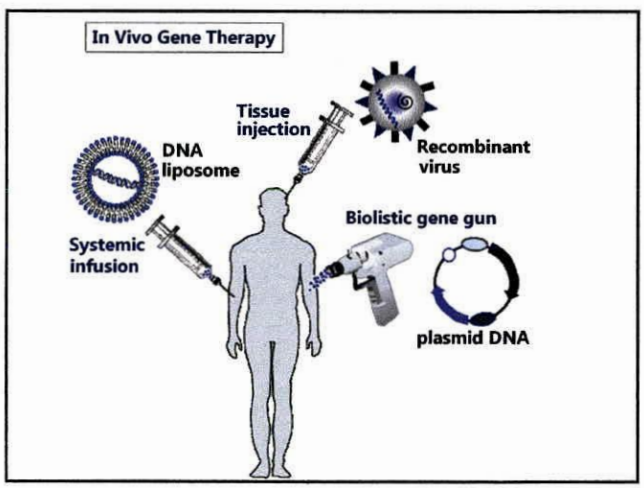
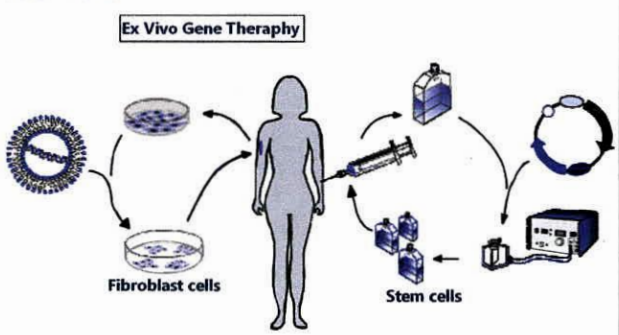


Ex-vivo



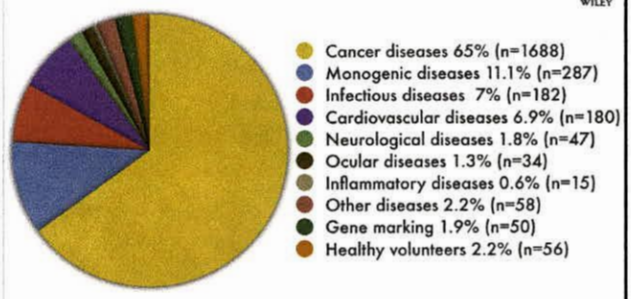
What factors have kept gene therapy from becoming an effective treatment for genetic disease? - I

- **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-lived 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 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.

Indications Addressed by Gene Therapy Clinical Trials



Ongoing Clinical Trials of Somatic Gene Therapy for Neurodegenerative Diseases (2009)

- Amyotrophic Lateral Sclerosis: 4
- Parkinson's Disease: 10
- Alzheimer's Disease: 3
- Diabetic Neuropathy: 5
- Multiple Sclerosis: 3
- Cubital Tunnel Syndrome: 1

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
- Adrenoleukodystrophy
- Primary dystonia
- Hallervorden-Spatz-Disease
- Spinal muscle atrophy

Animal model

Recent Research Highlights

- Neuroprotection
  - Administration of neurotrophic factors such as GDNF, BDNF, NGF,VEGF, IFG-1; promising in animal models for ALS, AD and PD (reviewed by Boucherie & Hermans, J of Neurosc Res. 2009;87)
  - Neuroprotective effects of BDNF in rodent and primate models of AD (Nagahara et al, Nature Medicine, Vol 15, March 2009)
- Gene knockdown approaches
  - RNAi for Huntington's disease (Comment by AR La Spada, Nature Med. Vol 15, March 2009), see next slide
  - Antisense oligo therapy for ALS1 (Comment by AR La Spada, Nature Med. Vol 15, March 2009)
- Gene replacement
  - Dopamine pathway in PD (reviewed by Brörklund &Kirik, BBA 1792 (2009)

Gene Therapy for Neurological Disorders by gene replacement

- Promising animal models
  - Mucopolysaccharidosis type VII (transfer of functional version of defect ß-glucuronidase gene)
- Michael Kaplitt, Weill Cornell Medical College in Ithaca, New York: Phase I clinical trial 2007 on Parkinson (http://www.medscape.com/viewarticle/558751):
  - Parkinson patients show reduced levels of GABA.
  - Injection of glutamic acid decarboxylase (GAD) gene for GABA-synthesis, using adeno-associated virus as a vector directly into the sub thalamic nucleus in 12 subjects,
  - Long-lasting gene expression of GAD gene,
  - No adverse immunological reaction, no brain toxicity,
  - Increase in GABA levels,
  - 30% improvement in brain function and well-being.

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

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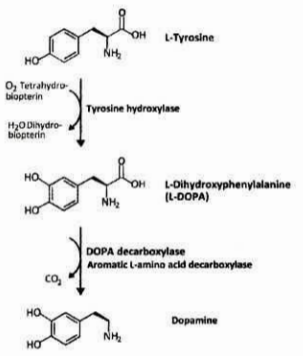


- In a macaque monkeys model of Parkinson disease, introduction of the three critical genes for dopamine synthsis (tyrosine hydroxylase, aromatic l-amino acid decarboxylase and guanosine 5'-triphosphate cyclohydrolase) into the striatum safely restored extracellular concentrations of dopamine and corrected 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)

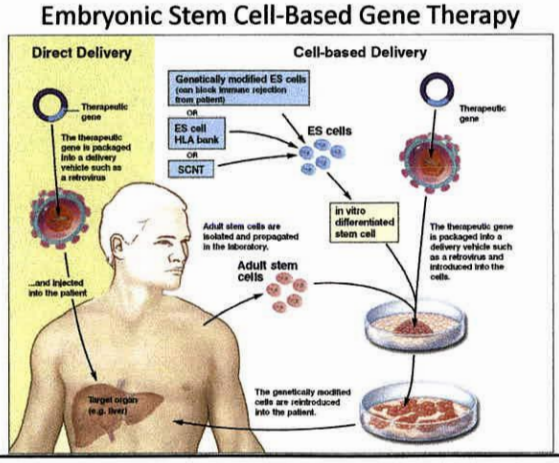
Huntington Chorea

- Huntington disease is a dominantly inherited genetic disorder in which one allele is abnormal while the other is normal.
- RNA interference or gene silencing may be a new way to treat Huntington's by targeting only the gene encoding the abnormal protein which will then not be produced.

Gene therapy for neurological disorders: Unique Challenges

- Targeting of the therapeutic gene
  - blood-brain barrier, cerebrospinal fluid delivery, specific brain region
- Ex vivo gene therapy and cell transplantation,
  - including use of patient-compatible, ES-cell-derived neurons
- Use of migratory cells
- Safety and efficiency of gene transfer
  - insertion into chromosome or autonomous existence outside of chromosome
- Proper regulation of these new genes
- Cost-effective gene therapy technology
- Combination therapy
  - gene therapy combined with enzyme replacement or cell transplantation

Embryonic Stem Cell-Based Gene Therapy



Observed and Possible Complications in Somatic Gene Therapy

- Acute side effects due to immune reactions to the vector
  - Somatic reactions
    - Fever, etc.
    - Drop in blood pressure
  - Psychological reactions
- Chronic side effects
  - Somatic reaction
    - Ongoing changes in the immune system
    - Secondary induced organ reactions
    - Cancer
  - Sperm or egg damage
  - Psychological and behavioral changes
  - Expectations not fulfilled

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 thought 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

- The effect on future generations raises a host of difficult questions and unknowns.
- Problem of enhancement even more pressing: Enhancement of future generations would be right-out eugenics and could result in new human types.
- Consent question: Can surrogate consent by one individual apply to all future generations?
- Safety aspects:
  - Inserted gene may produce adverse effects on development
  - The inserted gene may cause chromosomal damage to future generations
  - It would 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.
- In German ethical thinking germ-line gene therapy is inconceivable.

Somatic Gene Therapy for Enhancement of Brain Functions

- Memory, intelligence, emotions, motoric functions
- 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?

Physicians' Ethical Duties to Patients

- Prevent harm to patients (nonmaleficence)
- 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 with patience
- Avoid conflict of interest in patient care and research and adequately disclose those that cannot be avoided
  - Bernard IL, *Ethical issues in Neurology*, 2nd ed. Butterworth- Heinemann, 2002

Summary on Somatic Gene Therapy

- Doable
- 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"?

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

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
aneurosecr@med.auth.gr, www.neurology-delphi-2010

ΠΑΡΑΣΚΕΥΗ 5 ΦΕΒΡΟΥΑΡΙΟΥ 2010

FRIDAY 5 FEBRUARY 2010

9.00-9.30 Main Lecture

Chair: K.Jellinger, S.Baloyannis

F. Gerstenbrand, E. Heberle-Bors, G. Egger
Somatic Gene Cell Therapy in Neurology and Ethical Background

9.30-9.50 Lecture on neurogenetics and pathophysiology

T. Sclaviadis
Common pathways in Prion and Alzheimer's disease

9.50-10.10 Coffee break and poster viewing

10.10-10.40 Main Lecture

Chair. F. Gerstembrand, P.Kalvach

J. Toole
Neurological disorders in US Presidents - their effect on world events

10.40- 12.30 Round table on History of Neurology

Chairman F.Gerstembrand

F. Gerstenbrand:The development of European Neurology focused on the period of the separation
K.Jellinger: Highlights of Austrian Neurosciences in the 20th and 21st centuries
B.Lichterman: S.Shapovalova: Soviet Neuropathology (1917-1991).
S.Baloyannis: The Neurosciences in Byzantine Era
P.Kalvach: How lived our eponyms

12.30-13.30 Lunch