Term Paper Biology Class 4a

Gene Doping

1. Preface

1.1 Motivation: why did we choose this topic? We chose this topic because it's one of the most current topics, which has something to do with genetic engineering. Gene therapy is, although it could be very useful, only used for test persons because there could be a lot of unknown adverse reactions. Gene doping is based on the recent successful results in gene therapy but nobody knows if gene doping is already used or not. This topic deals with one of Darwin's Law; it's about surviving of the fittest. Of course sport is not about surviving but about winning, some athletes already have some genetic advantages, and therefore they are naturally better than the other ones and that's where gene doping comes into play. With gene doping the naturally disadvantaged can compensate it through inserting genes. So this topic also deals with ethics and fairness and we're both interested in these aspects of this topic.

1.2 What is especially interesting? Very interesting is that even the experts can't define gene doping exactly and even they don't know if some athletes already used it. A decision for gene doping changes the whole life of an athlete, he will be better in his sport and probably nobody will find out that he's gene doped but his life expectancy will decrease enormously and he can't change it anymore. So we think that's really an interesting point because gene doping is irrevocable.

1.3 What questions did we have in relation to the chosen topic?

- Is gene doping already a usual doping?
- Should everyone at the start of, for example, a race have the same possibility to win although there are a lot of differences between the fitness of the different participators?
- Are there any cases in which gene doping has been detected?
- How can the IOC prevent the use of gene doping?
- Is gene doping deadly?
- How does gene doping function?

2. Introduction

2.1 What is the context of the chosen topic? Are there any recent events? The World Anti-Doping Agency (WADA) defines gene doping as "the not therapeutic use of cells, genes, genetic elements, or the modulation of gene expression, having the capacity to improve athletic performance". This means that the athletes can improve their power with the help of the gene therapy. The advantage here is that the officials can't detect whether athletes have used gene therapy because their genetic advantage could also be natural. For example black people have a genetic advantage for sprints in their muscles, that's why so many black people win sprint races.

2.2 What is the (recent) scientific history? In 2001, the International Olympic Committee (IOC) had a meeting about the effects of gene therapy in relation to sport. After a few more meetings, the World Anti-Doping Agency (WADA) decided to prohibit gene doping. This was the first prohibition, which was made before this method of doping was known as being used. In 2005 the WADA had again a meeting on the topic "gene doping" and they shaped a declaration on gene doping, which included a strict demoralisation against gene doping. In 2006 a famous trainer named Thomas Springstein was condemned because he gave doping to young athletes and they also found an e-mail in which he asked a doping doctor for repoxygen, which is a gene doping and controls the ejection of epo; through epo the athletes have more red blood cells and so have a big advantage. They were not able to prove that Springstein really bought the repoxygen.

2.3 Where and why is the technique used? The main use for gene doping is in sport but it's not known whether it's already used because at the moment it's impossible to detect gene doping. The why is quite simply to explain, athletes want to improve their power and they want to win money, respect but also a place in history of sport. Through gene doping, athletes received a possibility to improve their power without being detected as dopers.

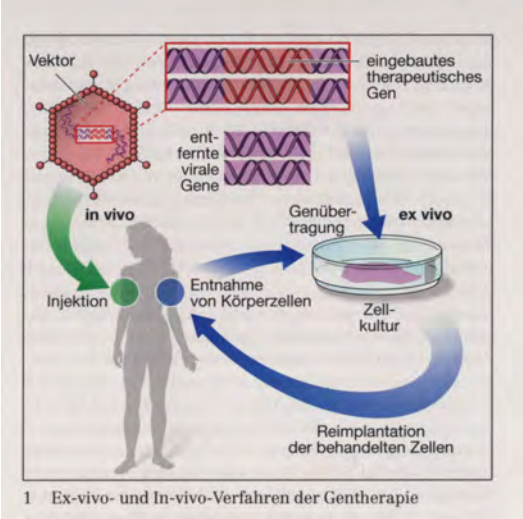
2.4 Are there alternative treatments? The alternative to gene doping is the regularly doping with injections but the IOC is able to detect these methods of doping and so this is not an alternative for athletes. The only alternative is to play fair and to refuse the use of doping.

3. Description of Engineering Technique

3.1 Explanation of the applied technique. Gene doping is a way of gene therapy and that's why we will explain four different ways of gene therapy.

First of all, there are some restrictions:

- Gene therapy can only be applied in one single disordered gene (monogenetic dysfunction) of which already exists a clonogenic cell.
- To prevent the inheritance of the new genetic information on the offspring of the treated individual, gene therapy is only applied in somatic cell, not on cells of the germ line (sperms, eggs).
- The transfer of a gene can be done on two different ways:
  - Directly inside the body of the receiver (in vivo).
  - Directly outside the body of the receiver (ex vivo).

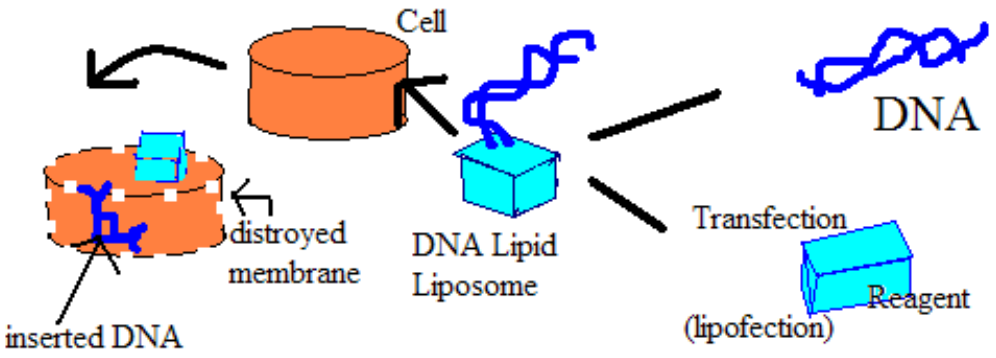


1 Ex-vivo- und In-vivo-Verfahren der Gentherapie

3.1.1 Ex-vivo and In-Vivo Method

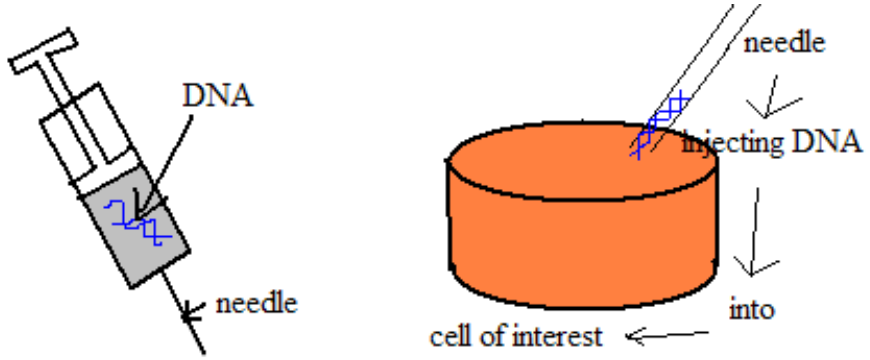
3.2 Methods

3.2.1 Transfection (chem.): The new improved genes combined with an electrical charged compound (i.e. calcium phosphate) are given to a cell. The electrical charged compound destroys the structure of the membrane of the cell, thus the new DNA is able to penetrate into the interior of the cell. (This method is not very efficient – success rate: 1:1'000 – 1:1'000'000.)



3.2.1.1 Process of Transfection (chem.)

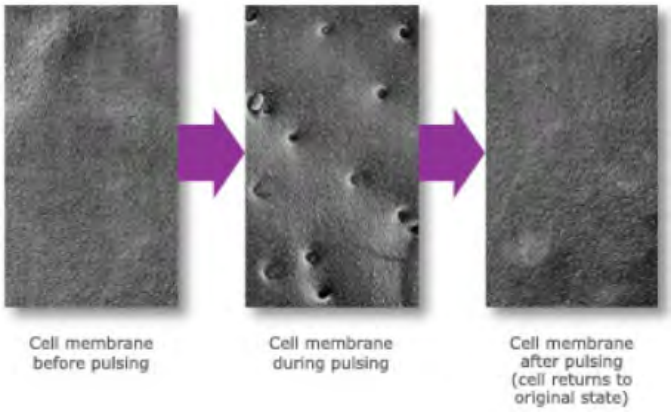
3.2.2 Transfection (phys.): With the aid of a very thin needle, the DNA is injected directly into the cell of interest. Every single cell has to be treated individually, so this technique is quite time-consuming, but it is more efficient than the chemical transfection.



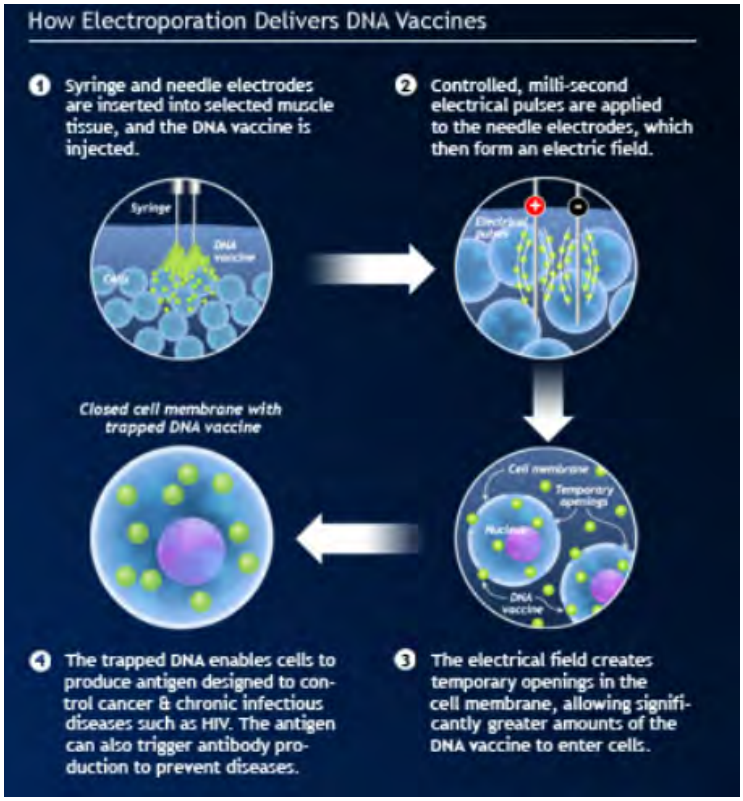
3.2.2.1 Process of Transfection (phys.)

3.2.3 Electroporation: While a current pulse makes the cell membrane porous, the DNA can easily enter the interior of the cell.

Note: This process can damage the cell fatally!

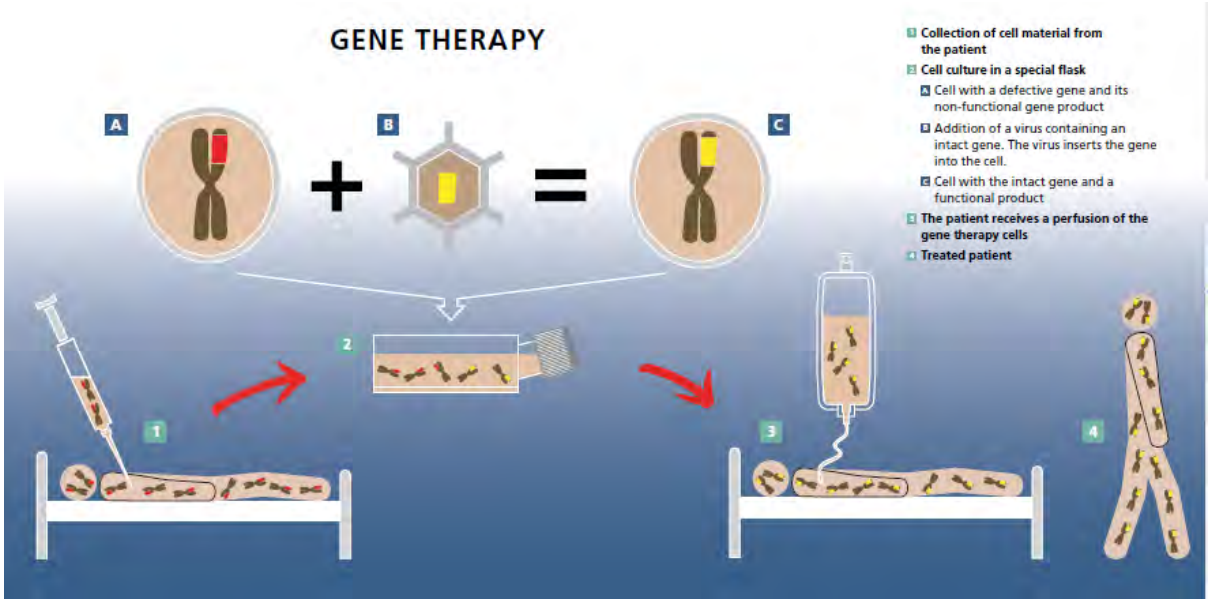


3.2.3.1 The Effect of the Current Pulse on the Cell Membrane



3.2.3.2 Process of Electroporation

3.2.4 Transduction: During this process, a genetically modified virus acts as a vector. The gene of interest is inserted into the cell by the virus. This method is the most suitable one for gene therapy. But, because this process is not very efficient yet, scientists have to take great amounts of viruses that lead to inflammation inside the body. But, the efficiency has increased, so there were already some successful treatments with this method.



3.2.4.1 Gene Therapy (Transduction; Virus as a Vector)

Appropriate cells for gene therapy have to have following characteristics:

- They should be taken out and reinserted easily out of and into the individuals' body.
- They have to survive the infection of the viruses.
- They have to be persistent so that they can produce proteins over a longer period of time.

Cell types:

hepatocyte, T-lymphocyte, bone marrow stem cells, muscle stem cells

3.3 Muscles and Gene Doping: Every type of sport needs another type of muscle. Scientists at the moment try to advance muscle growth for different types of sport.

3.3.1 General muscle growth: Some years ago, a boy with a lot of muscles was born. Professor Markus Schülke examined the muscle-boy, and he found out that this was caused by a mutation in the myostatin gene. Myostatin is an important gene for muscle growth and degeneration. It acts like a stop signal on stem cells in muscles, but in the case where myostatin is missing, muscles can grow uncontrolled bigger than normal. Today, scientists are able to apply this procedure to animals (see picture 3.3.1.1).

This discovery gives scientists a new hope for healing dystrophy (genetic disease, automatic degradation of muscles).

But of course, this could also be an option for gene doping.

3.3.1.1 left: wild type; right: treated mouse (without myostatin)

3.3.2 Buildup of a Muscle: Muscles consist of different bundles of muscle fibres, and each bundle consists of two types of muscle fibres. There are type-I fibres (slow twitch, slow contraction, dark red, slow tiring, good for staying power) and type-II fibres (fast twitch, quick contraction, bright colour, fast tiring, good for sprint). While training for the two disciplines, the used type of fibres will be built up more than the other one. This process could also be done by a genetic transformation. Scientists inserted PPAR (peroxisome proliferator-activated receptor) into the muscles of a mouse (to advance growth of slow twitch fibres) and like that, they created a kind of marathon mice.

3.3.3 Growth Factors: Growth factors are proteins (produced naturally in the body) that are important for the development of an organism. Either they are free and are transported through the blood stream or they are attached on the surface of a cell. Their function is to transmit signals when it comes to a contact with another cell, signals like an instruction to separate or to stop growing. To transmit the order, the growth factor bonds to the receptor cell molecule. This is a kind of lock-and-key-principle. Now, it's obvious that growth factors could be synthesized which happens already with hormonal doping. With gene doping, growth factors would be produced directly inside the body.

An example for a growth factor is IGF-1 (Insulin-Like Growth Factor 1). An experiment with mice shows:

- When inserted in adult mice, they still had a great muscle mass when they became older.
- When inserted into young mice, there muscle growth was more effective than in normal mice.

But: Although IGF-1 could increase muscle power; there are quite high risks (for i.e. cancer; see spread advantages/disadvantages).

3.3.4 Possible Types of Gene Doping

Name	Symbol	Possible application	Sport	Secondary Effect
Erythropoetin	Epo	Better condition (because of more red blood cells)	Condition athletes	Cancer; heart failure; liver and kidney degeneration
Vascular andothelial growth factor	VEGF	Better blood circulation and condition	"	Cancer; Angiogenesis
Growth hormone	GH	Muscle growth and regeneration	Condition athletes; power athletes	Inborn errors of metabolism

5. Discussion

5.1 What progress was made with the application of the chosen technique? Gene therapy is a very new and modern technique and is not totally developed until now. There were already some successful treatments, but there were also a lot of failures.

There were experiments i.e. to treat cancer, heart diseases or cardiovascular diseases, infectious diseases, monogenetic diseases neurological diseases and some other diseases.

So, gene therapy is a chance for sick people, but the fact that gene therapy enables scientists to replace a defect gene or to insert a missing gene, attracts some athletes. The chance is quite high that some of them want to misuse these methods for an improvement in performance. But, this technique is quite dangerous.

Risks:

There are two different ways of risks:

- adverse reaction during the transmission of the new genes
- adverse reaction of the new gene itself

During transmission: Most of all, viruses are used as vectors. Sometimes, in the body, viruses are treated as foreign bodies. Or the viruses are contaminated or not totally inactivated.

Adverse reactions of the gene itself: It can't be exactly controlled where the gene is inserted. Sometimes it adapts between two wrong sectors in the genetic make-up. Then, a gene could operate variedly because interaction between adjacent sectors is very important.

- Gene doping is more dangerous because it is accomplished with therapeutically impermissible agents.

- Gene doping is even worse than normal doping because it is irreversible.

5.2 What future research steps? About gene doping, there are probably a lot of illegal researches.

There is a law against gene doping although it can't be provided evidence. Scientists for instance Professor Bengt Saltin are looking for methods to prove the applications of gene doping.

5.2 Ethical Aspects, Advantages and Disadvantages

Pros	Contras
Every first class performance needs special genetic conditions. So, there would be only equal opportunities if every sportsman had the same genetic basics.	Equal opportunities don't mean that every athlete has the same genetic material (like machines). Equal opportunities mean that every person should make the best out of his natural skills.
If genetically favoured athletes are allowed, then genetically manipulated athletes should also be allowed.	The naturally favoured ones have recognised their advantage and then choose their sport. The genetically manipulated ones only want to improve their power and want to win, which is not in the sense of sport.
It's unfair to discriminate some genotypes, like it is unfair to discriminate an athlete because of its nationality, skin colour or religion.	Nobody is disqualified just because of his genetic features. Only if it's the case that this particular athlete has manipulated its genes.
Mankind has developed the gen engineering and so it is obligated to use it. The goal should be to improve mankind as a species.	Gene engineering is a great method to treat diseases but there are quite high risks. These risks are alright for a sick person but not for a healthy person, this is not ethical.
The improvement of mankind is something natural because evolution pursues the same goal.	Through evolution we can adapt ourselves better to the environment. We can not satisfy our interests of improving ourselves through evolution.
Athletes always want to improve their selves so it's better to let them do that legally under medical surveillance than illegally with a lot of risks.	To send young athletes without agreement into a medical adventure is not ethical. So education is very important for all the involved persons.

6. Summary in Facts

- Gene doping is a way to improve the athletic performance with the help of gene therapy.
- Gene therapy was originally developed to treat genetic diseases.
- Gene doping is prohibited by the World Anti-Doping Agency and can't be detected.
- It is more dangerous than hormonal doping because it's an irreversible process.

- There are four possible methods of gene therapy / gene doping. These four methods are:
  - Chemical transfection
  - Physical transfection
  - Electroporation
  - Transduction

- Possible risks/adverse reactions
  - During inserting the genes (because of still active viruses)
  - After inserting the genes (because of wrong interaction between the new genes and the body cells which probably leads to autoimmunity or cancer)

- One possible application of gene doping is to take out the myostatin gene (which normally acts as a stop signal after the muscle growth).
- Another option is to insert genes that produce growth factors for muscle cells (i.e. IGF-1).

- There are two different opinions when looking at ethical aspects:
  - Pro: All athletes should have the same genetic basics.
  - Contra: Everyone should make the best out of his natural skills.

References:

Books:

Gene Doping booklet from the “Bundesamt für Sport” (BASPO)

“Cornelsen Gesamtband”, p. 205

Internet:

http://www.dopinginfo.ch/

http://www.wada-ama.org/en/News-Center/Press-release/WADA-Gene-Doping-Symposium-Calls-for-Greater-Awareness-Strengthened-Action-against-Potential-Gene-Transfer-Misuse-in-Sport/

http://www.spiegel.de/wissenschaft/mensch/0,1518,314765,00.html

http://www.spiegel.de/wissenschaft/mensch/0,1518,305616,00.html

http://dasmagazin.ch/index.php/die-mutanten-greifen-an/

http://en.wikipedia.org/wiki/Gene_doping

Pictures:

- Picture 3.1.1: “Cornelsen Gesamtband” p. 205
- Picture 3.2.1.1: own creation; based on http://www.molecularstation.com/de/transfection/
- Picture 3.2.2.1: own creation
- Picture 3.2.3.1; 3.2.3.2: http://www.inovio.com/technology/howelectroporationworks.htm
- Picture 3.2.4.1: http://www.antidoping.ch/en/search/?q=gene+doping (online booklet)
- Picture 3.3.1.1: http://de.wikipedia.org/w/index.php?title=Datei:Muscle_Mouse_01.jpg&filetimestamp=20090821184518