

T O P I C A L P U B L I C A T I O N

# Gene Doping



NETHERLANDS CENTRE  
FOR DOPING AFFAIRS



# Gene Doping

PROF. DR. H.J. HAISMA

WITH CONTRIBUTIONS

FROM O. DE HON, P. SOLLIE

AND J. VORSTENBOSCH



NETHERLANDS CENTRE  
FOR DOPING AFFAIRS

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# Foreword

This is a new volume in the series of topical publications, published by the Netherlands Centre for Doping affairs (NECEDO). This series started in 1998 and has reported on the results of a wide variety of studies, ranging from the position of general practitioners in relation to doping related consults to the issue of mind sports and doping.

The topic of this latest publication is 'gene doping'. This subject has already led to numerous articles in the media, some of which were not hindered by a realistic image of the current state of affairs. This has led to a situation where some people regard the issue of gene doping as science fiction which might become a reality in the distant future, while others fear it as an imminent threat to the athletic world.

This subject has also led to questions asked to the Minister of Sport by members of the Dutch House of Parliament. In response to these questions, the Minister of Sport has invited the Netherlands Centre for Doping affairs to study this new phenomenon and to separate fact from science fiction. This study will also follow up on one of the recommendations made at the European Working Congress on Harmonisation and Future Developments in Anti-Doping Policy, held in Arnhem, the Netherlands in 2002, thereby contributing to the global effort in this area.

Gene doping has many aspects. It is, for example, conceivable that once genetic therapies have become commonplace in regular medicine, they may be very useful and acceptable for the athletic world as well (e.g. to treat injuries). However, the potential to abuse such therapies to enhance athletic performance in otherwise perfectly healthy individuals can be considered a threat. This report addresses all different aspects of gene doping and concludes with specific recommendations.

The subject of gene doping is surely an area where at the present there are many questions with not as many answers as we would like to have. But if the discussions (which are slowly beginning to develop) are continued, if research in this area is stimulated and if all relevant institutions will closely collaborate, I am confident that the athletic world will come up with fitting answers.

The principal author of this report is Professor Hidde Haisma, professor of therapeutic gene modulation at the University of Groningen and chairman of the Dutch Society of Gene Therapy (NVGT). The NVGT has been most cooperative since the first day that NECEDO approached them with questions regarding gene doping. I would like to thank Prof. Haisma and his predecessor in the NVGT Dr. Winald Gerritsen for their fruitful cooperation. The field of anti-doping is very broad and touches upon almost all fields of science. Therefore, I am very happy to include these two specialists in the advisory circle of the NECEDO.

I would like to thank you for your interest in this topic and wish that this report will be of benefit to all policy makers who will play a future role in tackling this new challenge in the field of doping in sports.

Rotterdam, February 2004

Jan Loorbach  
Chairman NEEDED

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# Summary

## Background

The Dutch Minister of Sport, Ms. Ross-van Dorp, has asked the Netherlands Centre for Doping affairs (NECEDO) for an inventory of the possible applications and risks of genetic manipulation in sports. Such an inventarization was requested by members of the Dutch parlement on the basis of, among other things, the gathering of the International Olympic Committee (IOC) on genetic engineering in June 2001, and the news that genetic manipulation could have already started, as stated by former speed skating champion and doctor Johann Olav Koss. In response to the Minister's request, NECEDO, in collaboration with the Dutch Society for Gene Therapy, organized an expert meeting to serve as the start of the inventarization for this report. At this meeting, representatives of the national and international scientific community discussed the possibilities of gene doping to improve athletic performance, health risks, applicability and preventive measures. In addition, a literature and internet search on the subject was performed and people from different disciplines in science and sports were interviewed. This report describes the results of the study.

## Gene therapy for sports doping

The elucidation of the complete human genome with approximately 30,000 different genes leads to new possibilities for diagnosis and prevention of a wide variety of diseases. In addition, this knowledge may be used for the design of new therapeutics, including gene therapy, based on the DNA sequence information. The principle of gene therapy is based on the delivery to a cell, of a therapeutic gene which may compensate an absent or abnormal gene. The genetic material (DNA) is mostly encapsulated and is introduced into the body by direct injection into the target organ. Gene therapy is currently an experimental therapy and its use is strictly regulated. In the Netherlands, clinical studies need approval from two offices: Central Committee on Research Involving Human Subjects (CCMO) and Committee on Genetic Modification (COGEM).

At this time, world wide (including the Netherlands) more than 3,000 patients have received gene therapy with very little side effects. Recent clinical data showed encouraging gene therapy results in patients with x-linked severe combined immunodeficiency disease, with 9 of 10 patients cured of their disease. Clinical studies in patients with hemophilia show promising results. In addition, angiogenic gene therapy with vectors expressing the human vascular endothelial growth factor, showed improvement in angina complaints and improved perfusion in ischaemia.

Gene therapy may not only be applied for the treatment of serious diseases, but also for less life threatening situations or injuries. Sports injury healing may be improved by gene therapy. In addition, athletes may be able to use gene therapy to



re-engineer their bodies for better performance. Many genes with potential to enhance athletic performance are available. The exact number of years that it will take for this method to enter the athletic arena is difficult to estimate, but it is most likely that this will happen within five years. The most relevant genes are Erythropoetin (Epo), Growth factors, Myostatin and Endorphins.

Gene doping is defined as 'the non-therapeutic use of genes, genetic elements and/or cells that have the capacity to enhance athletic performance'. The International Olympic Committee has included the method of gene doping in their list of prohibited classes of substances and prohibited methods per January 1st, 2003. The prohibited list of 2004, as published by the World Anti-Doping Agency, still includes the method of gene doping.

### **Risks of gene doping**

The risks involved in gene doping are several, and are related to the vector used (DNA, chemical, viral) and related to the encoded transgene. So far, gene therapy has been relatively safe; thousands of patients have been treated in well controlled clinical gene therapy trials with pharmaceutical grade gene therapy vectors and have shown few side effects. The therapy is confined to the patient with no transmission to offspring or next of kin.

With gene doping, gene transfer vectors may be produced in non-controlled laboratories. DNA can be easily and cheaply produced with materials available from legal suppliers. These preparations may be contaminated with chemicals and other impurities from the production and purification process, including pyrogens. Virulent viral gene therapy vectors may be produced which poses a major safety concern. In the case of virulent viruses, these are not only harmful to the athlete, but also pose a health risk for the general population who might get infected.

Health risks resulting from expressed genes are similar to those of other doping forms. However, the level and duration of protein production is less controllable when compared to conventional protein administration. For example Epo delivered by gene therapy could result in sustained high Epo levels which would increase the chances of stroke and heart attack.

### **Detection of gene doping**

Detection of gene doping is very difficult. Gene therapy vectors may be measurable only shortly after administration and in many cases would require tissue sampling. Taking muscle biopsies from athletes is no option, thus eliminating this form of detection. In addition, many forms of genetic doping do not require the direct injection of genes in the desired target organ. Finding the site of injection will be like looking for a needle in a hay stack. The protein resulting from gene transfer is not different from the endogenously produced protein and as such detection of the protein itself is no indication for doping. It will therefore only be possible to monitor the use of gene doping by repeated physiological protein profiling of athletes, allowing changes in protein levels to be perceived. These assays, which require the simultaneous measurement of many (possibly up to one thousand) different proteins and establishing ranges of normal values need to be developed.



## Preventive measures

Most athletes will not have enough background knowledge to fully understand the potential health hazards imposed by gene doping. Therefore, it is of utmost importance that athletes and their supporting staff will be educated on this subject in order to prevent the use of gene doping.

The pharmaceutical industry produces most currently used gene therapy vectors which may be applied for gene doping. To prevent these materials from entering the doping circuit, the industry should endorse a code of conduct stating it will not produce or sell products for gene doping. On the other hand, researchers throughout the world have easy access to genetic materials, including genes that may be used for sports doping. The research community, with the help of the different Gene Therapy Societies, should be encouraged to underwrite a similar code.

In order to develop an effective strategy for the prevention of gene doping, national as well as international coordination is required. The World Anti-Doping Agency should play a leading role. Coordination is necessary to set-up an educational programme for athletes and their supporting staff, as well as the general public. Also, research needs to be coordinated in order to investigate the development of methods to detect gene doping.

## Recommendations

### *1) Promote the development of detection methods at a global scale*

It is unlikely that a detection method for gene doping will be developed within the upcoming years. Methods either require invasive methods and show limited possibilities in itself or can only be realized through the full commitment of many parties. Current developments with proteomic techniques might provide a good basis for the development of a fail safe detection method. The scientific community should investigate and explore (new) possibilities for detection, preferably at a global scale. The World Anti-Doping Agency (WADA) would be the primary body to coordinate such an effort. Until a detection method for gene doping is developed the monitoring of athletes through regular blood sampling might provide an opportunity to screen for abnormal disruptions of the normal physiology – disruptions that might stem from gene doping. For this purpose existing monitoring methods, such as currently applied by the International Skating Union (ISU) and International Cycling Union (UCI), might be useful but perhaps new monitoring programmes are necessary.

### *2) Closely inform athletes on the potential consequences of gene doping*

The consequences of the misuse of genetic therapies for the purpose of sport enhancement can be severe up to life threatening. In an effort to be the best, athletes will push their boundaries. Some athletes even turn to doping and in a worst case scenario turn to alternatively produced doping (like THG) or experimental medication (like RSR-13). To prevent gene doping from becoming the doping of the athletes' choice, clear information for athletes and their supporting staff on its severe health consequences is needed. Elite athletes and athletes in gyms appear to be the primary target groups.

*3) Evaluate current regulations on genetic materials from a doping perspective*

The clinical use of gene therapy is strictly regulated in the Netherlands through the Genetically Modified Organisms Decree based on two European directives. However, the clinical application of gene therapy might differ in many ways from its application for doping purposes. For instance, gene therapy for doping purposes might be applied outside the regular clinical setting with the involvement of illegal laboratories. These differences justify taking a closer look at the current regulations on genetic materials.

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# I Introduction

The Dutch Minister of Sport, Ms. Ross-van Dorp, has asked the Netherlands Centre for Doping affairs for an inventory of the possible applications of genetic manipulation in sports.

The gathering of the International Olympic Committee on genetic engineering in June 2001 [Adam, 2001; Aschwanden, 2000], and the news that genetic manipulation could have already started, as stated by former speed skating champion and doctor Johann Olav Koss [Friedmann and Koss, 2001], prompted members of the Dutch parliament to ask the Ministry of Health, Welfare and Sport for an inventarization and possible preventive measures. Such an inventory also fits in the long term goals as outlined in the policy plan ‘Sport, Exercise and Health’ by the Minister of Sport. In response to the Minister’s request, the NECEDO, Netherlands Centre for Doping affairs, sought collaboration with the Dutch Society for Gene Therapy. In preparation of this report, an expert meeting was held on ‘Genetics & Doping’ at the Ministry of Health, Welfare and Sport on October 1, 2003. At this meeting, representatives of the national and international scientific community discussed the possibilities of gene doping to improve athletic performance, health risks, applicability and preventive measures. Representatives from the World Anti-Doping Agency (WADA) as well as NECEDO and the Ministry of Health, Welfare and Sport were present. This expert meeting served as the start of the inventarization for this report.

## 1. 1 Objectives

This report aims to describe the possibilities of gene doping for improving athletic performance.

Aspects of gene doping
Potential to enhance athletic performance
Potential health risks
Applicability in an athletic setting
Preventive measures

In this report first doping and gene doping are defined with relevant background in genetics and gene therapy. Then the possibilities of gene doping to improve athletic performance, health risks, applicability and preventive measures are discussed. Several examples of possible gene doping products are discussed in more detail. It is envisaged that the current report will constitute a firm basis which can be used for policy making and for continuous monitoring of this issue in the future

## 1. 2 Research methods

Representatives from NEEDED and the Dutch Society for Gene Therapy first met in the spring of 2003 to discuss the use of genetic manipulation in sports. It was decided that there was a great need for an up-to-date overview of the possible use of gene doping to improve athletic performance. To obtain insight in the possibilities of gene doping for improving athletic performance, an expert meeting was organized in which experts from different disciplines were asked for their views on specific genes that may be used for gene doping. This information served as a starting point to further deepen the study by performing a literature and internet search on the subject. In addition, people from different disciplines in science and sports were interviewed in order to obtain an idea of the notion and possible impact of gene doping.

## 1. 3 Previous reports and meetings

The discussion on gene doping was initiated in June 2001, when the Gene Therapy Working Group, convened by the Medical Commission of the International Olympic Committee (IOC) had a meeting on the theme 'Gene therapy and its future impact on sport'. This committee concluded:

'We endorse the development and application of gene therapy for the prevention and treatment of human disease. However, we are aware that there is the potential for abuse of gene therapy medicines and we shall begin to establish procedures and state-of-the-art testing methods for identifying athletes who might misuse such technology. This will require investment in modern detection methods including antigen detection, gene chip and proteomic analysis which are now becoming available. We are confident that we shall be able to adequately monitor abuses and establish the procedures for doing so using ethically acceptable methods.' [Cummiskey, 2002]

The World Anti-Doping Agency (WADA) has convened a conference on this issue in March 2002 [Pound, 2002] and it also was one of the main topics of the 'European Working Congress on Harmonization and Future Developments in Anti-Doping Policy' in Arnhem, the Netherlands in April 2002. The results of these discussions were a call for a worldwide effort to deal with this new sort of doping and especially a joined effort of scientists, medical doctors, governments, anti-doping organizations, and the pharmaceutical industry to exchange all relevant information including educational ideas, research results and detection methods on this potentially new technique for doping.

The International Olympic Committee (IOC) has included the method of gene doping in their list of prohibited classes of substances and prohibited methods per January 1st, 2003. Starting in 2004, WADA has taken over the responsibility to publish an international doping list [WADA, 2003]. The method of gene doping is still included.

## 2 Doping

Athletic performance may be increased in many ways, some of which are permitted and some of which are prohibited by the governing sports bodies. An example of the latter is the use of performance-enhancing drugs, or doping. Doping can be both of chemical and protein nature or may involve prohibited methods, such as illegal blood transfusions. A survey from the Centre for Drugs Research [Abraham et al., 2002] concluded that less than 1% of the Dutch population has ever used doping products, a total of approximately 100,000 people. Forty percent of these people use doping on a yearly basis, the majority of which is active in strength training or body building.

The prevalence of doping use in elite sports (athletes performing at the level of international championships) is likely to be higher than the mentioned 1% in the general population, but an exact percentage cannot be given. The percentage of athletes that test positive in doping tests has oscillated between 1.3% and 2.0% over the last few years [DOCONed, 2002].

The past has shown that some athletes (and their entourage) go great lengths to gain a competitive edge. Pharmaceutical products have been found that had not yet been sufficiently tested for side effects (as was the case with efaproxiral or RSR-13 in 2001) or that have been produced specifically for the use by athletes, without even knowing possible side effects (which was proven by the discovery of tetrahydrogestrinone or THG in 2003). This shows that even when it can be expected that the use of certain products will have serious health consequences, some athletes are willing to serve as subjects in an uncontrolled trial.

### 2. 1 Gene doping

According to WADA, gene or cell doping is defined as ‘the non-therapeutic use of genes, genetic elements and/or cells that have the capacity to enhance athletic performance’ [The World Anti-Doping Agency, 2001]. This definition leaves room for questions. What exactly is non-therapeutic? In the future it may be possible to treat patients with muscle disorders by genetic medicines that will improve their muscle strength. Will these patients be allowed to perform? The same holds true for patients who were treated for cancer by chemotherapy and now receive a gene encoding Epo to boost recovery of the bone marrow but may also increase their hematocrit levels. Studies have also been conducted to speed up wound healing and to ameliorate muscular soreness after exercise, a practice that might not be considered as ‘therapeutic’ by everybody and their performance enhancement properties might be questionable. Once genetic therapies have become commonplace, it will not be fair to deny these therapies to all athletes. From a clinician’s point of view It would be better to specify the definition of gene doping so it will solely address the unapproved use of genetic transfer technologies.



## 2. Ethical aspects

The general ethical justification for the prohibition of gene doping by WADA is given in section 4.3. of the World Anti-Doping Code (version 3.0, 20 February 2003), in which the criteria are given for including substances and methods on the so called Prohibited List. Besides the criterion that 'there is scientific evidence, proven pharmacological effect or experience that substances or methods included have the potential to enhance or enhances sport performance', two main ethical arguments are given for including substances or methods on the doping list.

First, the use of the substance or method is causing an actual or potential health risk to the athlete. The underlying ethical principle is to protect individuals against harm or risk to health. The second argument is that the use of doping violates the spirit of sport. This spirit of sport is described in the introduction to the Code with reference to a rather miscellaneous set of values such as ethics, fair play, honesty, health, fun and joy and respect for rules. Many of these values are not specific for the practice of sports and the application of these values to the issue of doping is often ambiguous.

We take it that 'fair play' comes closest to the intrinsic value of the spirit of sports. This value is reflected in an organized equality of conditions, which athletes implicitly endorse and under which athletes compete with one another. This value, in turn, is justified by values and considerations which are deeper embedded in the meaning and sense of sports as a human practice to be conducted in ways that are recognizably human and humane. No mention is made in the Code of the often used argument of 'cheating' by users of doping. The argument goes that the use of doping is morally wrong because it deceives other athletes and organizations concerning the means which athletes use to compete. Presumably this argument is not used because in the context of the Code, reference to the argument of 'cheating' begs the question whether doping ought to be prohibited in the first place. However, if the code is effectuated and constitutes a recognized set of rules for athletic competition, this argument is valid as a moral argument directed at individual athletes who have placed themselves under the rules of the practice and organization. From now on, we concentrate on the health argument and the fair play argument.

In reference to evidence described elsewhere in this report, it is clear that gene doping can be dangerous and detrimental to health. The case of gene doping is special in the sense that there are many uncertainties as to the long-term effects of gene modifications. Many of these effects may go unnoticed because they never might be studied in a scientifically reliable way for financial reasons, or for the reason that it is difficult to define reliable paradigms for the study of side-effects of completely new methods or new applications. This argument applies to the administration of genetically modified substances, as is now already practicable. But it applies especially to the application of gene 'therapy' for purposes of improving 'bodies' to compete in sports. In contrast to somatic cell therapy, germ-line alterations are permanent and are transmitted to future generations. In addition to the possibly grave risk for the health of athletes, the uncertainties with respect to effects create moral problems concerning responsibilities with regard to third parties such as off-spring, parents and partners and with regard to informing the athlete in a way that makes risk-acceptance by the athlete him- or herself a possible way of justifying the use of these substances and methods.

The aspect of fair play might be compromised by gene doping in an especially deep and potentially disastrous way for the practice of sports. In the area of pharmacogenetics, which is being developed rapidly by the combined efforts of science and the pharmaceutical industry, the objective is to develop 'tailor-made' medicines for individuals. As is well-known, many drugs have quite a different effect on individual people because they are developed and defined in a general way and not in view of the differential genetic dispositions of individuals to respond to substances. Therapeutically, pharmacogenetics is a very promising area. However, if the knowledge that becomes available is used in sports, the very idea of a competition between athletes who are recognizably equal and prepare themselves in more or less comparable ways, might become obsolete. The arguments against doping in the 'old' (chemical) sense might all come in here with extra force. These arguments are that doping makes competition dubious and unreliable, because the test of relative inequalities based on one's own individual bodily efforts, talents and character is perverted. 'Tailor-made' substances and methods might help the individual athletes to make the best of their abilities, but it will make sport as an essentially social and collective practice uninteresting and even no longer human-like, in the sense that people might no longer be able to identify with the human characteristics and actions of athletes and their performances, but will come to see them as manufactured 'products of science'.

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## 3 Gene therapy

### 3. 1 Genes

The human genome represents the whole genetic information of each individual. This information resides on the chromosomes (23 pairs), which are present in each nucleus of all the cells that make up the organs. The chromosomes contain DNA (DeoxyriboNucleic Acid) which is a double helix composed of four bases (A=adenine, G=guanine, T=thymine and C=cytosine). The genetic information is determined by the sequence of these bases in a chain of nucleotides. This sequence determines the order of amino acids to create a specific protein, such as enzymes or structural proteins. The sequence information that is necessary to obtain one specific protein is called a gene.

The elucidation of the complete human genome with approximately 30,000 different genes will lead to new possibilities for diagnosis and prevention of a wide variety of diseases. In addition, this knowledge may be used for the design of new therapeutics, based on the DNA sequence information.

Genomics is the study of genes and their function, which includes genome mapping, gene sequencing and gene function. One way to study the genome is by DNA-chip or gene array; a microchip that holds DNA probes that form half of the DNA double helix and can recognize DNA from samples being tested. DNA chips are widely used to study the composition and activity of different genes under different circumstances, including disease and fitness. One such chip may hold up to 30,000 genes and thus covers almost the complete human genome.

Pharmacogenomics is the study of the interaction of an individual's genetic make-up and response to a drug. People differ in their response to drugs. Some people may lack a receptor that the drug is interacting with whereas other people may have an enzyme that rapidly degrades the administered drug. Pharmacogenomics will allow a better fine tuning of drug administration for patients based on their individual gene make up. This will not only diminish side effects because of optimal dosing, but will also improve the outcome of treatments because patients will get tailor-made treatments.

People from different ethnicity have a different genetic make-up which results in differences in susceptibility to certain diseases. People from African descent, for example, are more prone to Sickle Cell anemia and among people from Jewish origin the hereditary disease Tay-Sachs (childhood dementia) is more common.

### 3. 2 Genes and sport

'Athletes are not born equal' is a controversial quote from Sir Roger Bannister, the first man to run the one mile under 4 minutes. People from specific ethnic origin seem to have an advantage over others. West-African runners dominate the short

distance running whereas athletes from East Africa do well in the marathon. On the other hand, Caucasians dominate in swimming contests.

In this age of genetics and genomics, it will be possible to elucidate the genes that predetermine ones predisposition for a specific sport [Rankinen et al., 2001; Rankinen et al., 2002]. Genetic screening at early age may indicate the greatest potential for a specific child to develop into a top athlete and a specific training programme may be designed. On the other hand, genetic screening of athletes may be used to select specific training methods to enhance or improve his or hers genetic predisposition [Rankinen et al., 2001; Rankinen et al., 2002].

Will these screening methods result in better athletes? Marion Jones and Tim Montgomery are both record holders for the 100 meters sprint. They had a baby in the summer of 2003. This child will certainly have a genetic advantage over many other babies born but other aspects such as psychological and environmental factors will ultimately determine whether this child will be a top athlete.

### 3. 3 Gene therapy

Gene therapy may be defined as the transfer of genetic material to human cells for the treatment, or prevention of a disease or disorder. Genetic materials can be DNA, RNA or genetically altered cells.

The principle of gene therapy is based on the delivery to a cell, of a therapeutic gene which may compensate an absent or abnormal gene. In general, DNA is used as the genetic material. This genetic material encodes for a therapeutic protein and needs to be delivered to the cell nucleus to be active. In order to deliver the genetic material, this material can be encapsulated into a virus such as adenovirus or retrovirus or into a lipid such as a liposome. The viruses are crippled so that they are no longer pathogenic. The encapsulated genetic material is mostly referred to as a vector and is introduced into the body by direct injection into the target organ or administered by aerosol for lung delivery. Also, it is possible to isolate cells from a patient and treat these cells with the vector in the laboratory and then reimplant these into the patient.

The DNA encodes for a protein which will give the therapeutic effect. In the DNA, sequences are present that turn on and off the protein expression, the promoters. Depending on the nature of the promoter and the vector used for delivery, the protein expression may be of short (days-weeks) or long (weeks-years) duration. The expressed protein may be confined to the cell that was treated, or in the case of a secreted protein, the protein may travel from the cell into the surrounding tissue or into the circulation.

At this time, more than 3000 patients have received some form of gene therapy, with very little side effects. In the Netherlands, most university hospitals are engaged in gene therapy studies, with hundreds of patients suffering from different diseases, ranging from cancer to heart failure, treated. Recent clinical data show encouraging gene therapy results in three major diseases: patients with x-linked severe combined immunodeficiency disease [Hacein-Bey-Abina et al., 2002] and patients with hemophilia B [Kay et al., 2000]. In addition, angiogenic gene therapy with vectors expressing the human vascular endothelial growth factor for the treatment of coronary artery disease, showed improvement in angina complaints [Losordo et al., 1998]. These studies show that gene therapy is a safe treatment, capable of curing

patients with, in some cases, life threatening diseases with no other treatment alternative available.

Currently, there is only one registered pharmaceutical product based on gene technology, several other products are experimental and are administered in a research setting in hospitals. The only registered product is based on anti-sense technology, which is a piece of DNA complementary to the DNA of a virus which will block the replication of this virus. This is used in eye-drops for the treatment of Cytomegaly Virus infections.

### 3.3.1 Regulations

In the Netherlands, clinical use of gene therapy is strictly regulated. Clinical studies need approval from two offices: Central Committee on Research Involving Human Subjects (CCMO) and Committee on Genetic Modification (COGEM).

The European directives 90/219/EEC and 90/220/EEC are implemented in the Dutch legislation through the Genetically Modified Organisms (GMO) Decree. The GMO office prepares permits pursuant to the Genetically Modified Organisms Decree. It is the contact point for information concerning permit applications. The final decision on permits is the responsibility of the Ministry of Housing, Spatial Planning and the Environment (VROM). The GMO office handles requests for advice on applications for permits pursuant to the Environmental Management Act in consultation with the COGEM. The GMO office is part of the Centre for Substances and Risk Assessment (CSR) of the National Institute of Public Health and the Environment (RIVM).

The CCMO oversees medical research involving human subjects in the Netherlands. Research involving human subjects must first be assessed in terms of medical ethics. Researchers can obtain an approval to perform the research from a recognized review committee or, in certain cases, from the CCMO. The CCMO was established on 6 April 1999 and is based in The Hague.

In most European countries, including the Netherlands (Embryo Law, article 24 sub g), gene therapy is only permitted in somatic cells, which are all cells in the human body except reproductive sperm and egg cells. Therefore, this form of gene therapy will not affect future generations.

### 3.3.2 Vector production

As described in the previous section, gene therapy is delivered by vectors, which may be of biological origin in the case of viruses or chemical compounds such as liposomes. The preparation of DNA itself is relatively simple. The DNA containing the gene encoding the desired protein such as a growth factor, can be obtained from commercial sources covering almost the entire human genome or may be isolated with routine molecular biology techniques. The DNA can be produced in large quantities in bacteria, in the form of a plasmid, which is a piece of circular DNA. Bacteria are easy to grow at low costs. Then the DNA can be purified with commercially available kits. The whole production process for DNA takes only 1-2 days and results in a pure preparation which may be used in patients after safety testing.

The preparation of liposomes and other chemical vectors starts with the production of DNA, which is then followed by the addition of the chemical compounds,

which serve to improve the cellular uptake of the DNA. Depending on the methods used, several purification steps are needed to obtain an injectable product. Because all ingredients are relatively pure, this procedure is easily scaled up to pharmaceutical grade and scale.

In contrast to plain DNA or chemical vectors, the viral vectors are much more efficient in gene delivery, but impose a more difficult production method. The viruses are produced in cell lines of murine or human origin. These cell lines need to be cultured under specific conditions to allow the viruses to be produced. The virus is then harvested and purified from the cell debris and culture supplements. In some cases the crippled virus containing the desired gene may be contaminated with recombinant wild-type virus, which is of potential danger for patients and needs to be avoided. Therefore, care is taken into analysis of the virus produced, to define the possible contamination.

The costs for production of gene therapy vectors highly depend on the vector used. The simplest systems, starting with plain DNA, are obviously the cheapest to produce, whereas the more complicated vector systems such as the viral systems are the most expensive. For a large part, the costs are due to the many safety precautions and testing that is performed on clinical batches.

## 4 Gene therapy for sports doping in an athletic setting

Gene therapy at this time is an experimental therapy for serious human diseases. Clinical data showed encouraging gene therapy results in patients with x-linked severe combined immunodeficiency disease [Hacein-Bey-Abina et al., 2002] and patients with haemophilia B [Kay et al., 2000]. In addition, angiogenic gene therapy with vectors expressing the human vascular endothelial growth factor for the treatment of coronary artery disease, showed improvement in angina [Losordo et al., 1998]. Despite these early positive results, it may be years before gene therapy is a standard treatment for one of these diseases.

### 4. 1 Sports injuries

In the future, gene therapy may not only be applied for the treatment of these serious diseases, but also for less life threatening situations or injuries. Sports injuries usually involve tissues that display a limited capacity for healing. Treatment of various sports-related injuries, including muscle injuries, ligament and tendon ruptures, central meniscal tears, cartilage lesions, and delayed bone fracture healing is labor intensive and time consuming. Gene therapy using the transfer of defined genes encoding suitable growth factors into the injured tissue may potentially result in improved regeneration of tissue defects following trauma [Huard et al., 2003]. These approaches are currently being evaluated in animal models. It may be expected that clinical studies will follow in the coming years.

### 4. 2 Gene therapy for sports doping

Athletes may be able to use gene therapy to re-engineer their bodies for better performance. Many genes with potential to enhance athletic performance are available (see table below). The most relevant are discussed in more detail. These genes not only have potential to improve athletic performance of human athletes. Also in animal sports, such as horse racing, gene doping may be applied. In this report however, the discussion will be limited to human athletes.

Potential is defined as the relative ease to use the gene in an athletic setting in relation to the expected effect.

Range:

++++ easy to use, great potential,  
- difficult to use, little effect expected.

Risk is the health risks for the user when such a gene is introduced.

Range:

++++ potentially very dangerous for health,  
- no health effects expected.

Risks are discussed in Chapter 5. Controlled risk is in the case of pharmaceutical grade gene transfer vector use, with the appropriate safety testing. Uncontrolled risk is when gene therapy vectors are produced in uncontrolled laboratories, with no assurance of quality control or safety testing.

Genes	Potential	Risks controlled	Risks uncontrolled
Erythropoietin (Epo)	++++	+/-	++++
Insulin-like growth factor (IGF-I)	++	+	++++
Vascular endothelial growth factor (VEGF), Fibroblast growth factor (FGF)	+	+/-	++++
Growth hormone (GH)	+	+	++++
Myostatin / follistatin	++++	?	++++
Endorphins, enkephalins	+	?	++++



#### 4.2.1 Erythropoietin (Epo)

In 1964, Finnish Nordic skier Eero Mäntyranta blew away the competition and won two gold medals at the Olympic Games in Innsbruck, Austria. It was later shown that Mäntyranta had a naturally occurring genetic mutation that gave him higher amounts of red blood cells than the average person. Having more red blood cells means more cells to carry oxygen from the lungs to tissues, thus increasing his endurance. Mäntyranta had what every endurance athlete wants and what Epo can provide. Athletes of the future may be able to alter their genes in a way that mimics the natural mutation that Mäntyranta had.

This may be accomplished by inserting an additional copy of a gene into a person to boost production of the hormone erythropoietin (Epo). This hormone instructs the body to manufacture new red blood cells, which, in turn, increases aerobic capacity. Patients who suffer from severe anemia, such as people with AIDS, cancer patients after chemotherapy or patients with kidney failure, may benefit tremendously from this form of therapy because their bodies produce inadequate amounts of red blood cells. For athletes, increased Epo production would enhance oxygenation of tissues, in turn increasing endurance.

Epo may be delivered as a protein by injection, or by introduction of the gene encoding Epo into the body's cells. Researchers successfully delivered Epo genes into the cells of mice and monkeys. The hematocrits (the proportion of blood volume made up of red blood cells) of the animals were boosted by as much as 80 percent [Zhou et al., 1998]. When adeno-associated virus was used for Epo gene delivery into monkeys, the animals developed supraphysiologic levels of Epo and polycythemia. However, a severe anemia ensued in some animals due to an autoimmune response to endogenous and transgene derived Epo. This inadvertent autoimmunity has not been observed in other studies, but may pose a serious problem if it would develop likewise in humans [Gao et al., 2003]. Given these unexpected side-effects, it will be several years before Epo gene therapy will be evaluated in clinical studies.

#### 4.2.2 Insulin-like growth factor-I (IGF-I)

Like gene therapy for Epo production, techniques to strengthen muscles are being developed to help people with illnesses: in this case, people with degenerative muscle conditions such as muscular dystrophy. Whereas the Epo therapy would be pervasive throughout the body, this approach would target specific muscles. Insulin-like growth factor-I, IGF-I, is made in the liver as well as muscle and has anabolic effects. Its concentration is related to the concentration of growth hormone (GH). IGF-I gives rise to an increase in muscle bulk in mice injected with the gene [Barton-Davis et al., 1998]. This was in the absence of any special exercise programme. Extending this treatment to athletes could mean strengthening a tennis player's shoulder muscles, a sprinter's calves or a boxer's biceps. Such gene therapy is likely to be relatively safe given that the effects seem to be localized to the targeted muscle and is likely that human trials will start in the coming years. Combining IGF-I with other growth factors or with strength based training programmes may lead to even greater responses in muscle growth. However, before clinical studies can be started, further studies in primates need to be performed to further evaluate the efficacy and toxicity of IGF-I for gene therapy.

#### 4.2.3 Vascular endothelial growth factor (VEGF)

Genes may also be used to help grow new blood vessels. This therapy is being developed to produce a coronary bypass in patients with ischaemic heart disease and may help elderly people with peripheral arterial disease, which is the death of tissues in the body's extremities because of inadequate oxygen supply. The gene encoding vascular endothelial growth factor (VEGF) or other factors may turn on the formation of new vessels. Clinical studies are being performed all over the world, including in Groningen, the Netherlands. These clinical trials in many instances show efficacy in patients with angina [Losordo et al., 1998; Losordo et al., 2002] or peripheral arterial disease [Baumgartner et al., 1998; Losordo et al., 2002; Rajagopalan et al., 2003]. If athletes used these treatments for improving blood vessel production, the result could be a hyper supply of oxygen and other nutrients to the tissues. With better supply lines, muscles, lungs, the heart and other parts of the body would not tire as easily. As VEGF is already used in several clinical studies, VEGF gene doping would be possible at this time with the gene therapy vectors used in those studies.

#### 4.2.4 Myostatin

Myostatin is a negative regulator of muscle formation. Synthesized by muscle cells it acts either auto- or paracrine in heart and skeletal muscle. Its physiological role is still not yet clear. Administration of myostatin blockers such as follistatin, mutant activin type 2 receptors and myostatin propeptide, will result in a dramatic and widespread increase in skeletal muscle mass due to an increase in number of muscle fibres (hyperplasia) and thickness of fibres (hypertrophy) and less fat and connective tissue in muscle [Lee and McPherron, 2001]. These myostatin antagonists may improve muscle regeneration in patients suffering from Duchenne and Becker muscular dystrophy [Bogdanovich et al., 2002]. At this time myostatin inhibitors are advertised to boost muscle size without exercising. Athletes could use these agonists as gene doping in the near future.

#### 4.2.5 Endorphins

Pain is a warning sign and should not be ignored. Muscular exhaustion leads to a hyperacidity because it uses up so much energy and prevents the detoxication of the lactic acid, the waste products of matrix and causes pain. Pain relief could potentially help athletes to perform better or for a longer period of time. Most athletes will use an over-the-counter pain reliever at some time. These drugs, in fact, are some of the most widely used drugs. An alternative to these chemical drugs could be analgesic peptides such as endorphins and enkephalins. The genes encoding for these peptides could be administered and may be used for pain relief. At this time, preclinical animal studies have shown that genes encoding for such peptides have an effect on inflammatory pain perception [Smith, 1999; Lin et al., 2002]. Although promising, pain relieve gene therapy is still in its infancy and far from clinical application.

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## 5 Risks of gene doping

Gene therapy is currently an experimental therapy delivered to patients in a well controlled setting. The gene transfer vectors used have been produced in certified laboratories and have been extensively tested for toxicity and safety. If gene therapy would be used to improve athletics performance it is very likely that such a setting will be absent.

### 5. 1 General health risks

The risks involved in gene doping are several, and are related both to the vector used (DNA, chemical, viral) and to the encoded transgene. So far, clinical gene therapy studies have been relatively safe. Over 3000 patients have been treated and only one patient died due to a chronic liver disease and an over-dosing of vector [Raper et al., 2003]. In two other patients, who were cured for their life-threatening immune deficiency disease, leukemia-like symptoms developed [Hacein-Bey-Abina et al., 2003].

Recently an autoimmune response to endogenous and transgene derived protein was reported in monkeys. Adeno-associated virus was used for Epo gene delivery and some animals developed a severe anemia due to an autoimmune response [Gao et al., 2003]. So far, this inadvertent autoimmunity has not been observed in other studies, but may pose a serious problem if it would develop likewise in humans.

Other side effects from gene therapy that have been reported are mostly flu-like symptoms. There have been no reports on transfer of gene therapy vectors from treated patients to next of kin or to germ cells [Griscelli et al., 2003; Tenenbaum et al., 2003; Arruda et al., 2001].

However, if gene transfer vectors would be produced in non-controlled laboratories, the preparations may be contaminated with chemicals and other impurities from the production and purification process, including pyrogens and virulent viruses. The potential for generating new viruses, known as replication-competent viruses (RCV) is a major safety concern. There is no way to predict the virulence or disease potential of recombinant viral vectors. These impose great safety risks for the people who would receive these agents.

### 5. 2 Specific health risks

Health risks related to the specific proteins expressed in gene doping are similar to those of other doping forms. Healthy people who unnaturally boost their Epo levels increase their chances of stroke and heart attack because adding red blood cells makes the blood thicker. As it gets thicker, it becomes more difficult for the body to pump it successfully to all tissues of the body, causing clots wherever vessels cannot compensate for this increased density. Whereas the athletes using synthetic Epo today face similar risks, after a few weeks the risk subsides as Epo is cleared from the

body and red blood cell production returns to normal levels. But if Epo would be delivered by gene therapy, the level and duration of Epo production is less controllable. The hematocrit would be less manageable and could continue almost indefinitely giving rise to pathological Epo levels.

Other genes may give different health risks if the expression is not controlled. It may be envisioned that genetic growth hormone treatment with IGF-I or VEGF may give rise to tumor development. Therefore, it is crucial that selected pharmaceutical grade gene delivery vectors are used, which will have a known and controlled gene expression pattern.

## 5. 3 Environmental risks

Athletes that would have received gene therapy may have genetically modified cells or excreta that contain the gene transfer vector. This may potentially pose a risk for people in close contact with the athlete, because they may be exposed to the gene. In current gene therapy trials, patients treated with viral gene therapy vectors are closely monitored for shedding of the gene therapy vectors and in most instances should have no detectable gene therapy vector in blood, stool, urine, semen, or saliva before they are allowed to leave the hospital. Although there have been no reports of unwanted gene transfer from shed gene therapy vectors in clinical studies, this can not be excluded when athletes are treated with these vectors in a less controlled environment.

## 6 Detection of gene doping

A concern in the athletic community, especially among doping control agencies, is that no one knows how easily gene doping can be detected, if at all.

The DNA which is used for gene transfer of the gene is of human origin, and therefore not different from that of the person applying gene doping. Labelling of gene transfer products with genetic 'bar codes' as has been suggested with Genetically Modified agricultural produce may be an option however this would require the complete cooperation of scientists, ethicists, athletes, sports authorities, medical practitioners, professional societies, pharmaceutical and biotech industries, and the public to avert misuse.

Gene doping will be delivered by a vector containing DNA, with or without chemicals to enhance gene transfer or by a viral vector. Muscle based therapies will be confounded to the injection site or tissue in the direct vicinity. Therefore, many of the muscle based gene technologies are unlikely to be detected by urine or blood testing as is currently done in elite athletes. The detection of associated chemicals or viral particles may be of use but this would involve tissue sampling. It will be unlikely that athletes can be forced to give consent to this procedure given the invasive nature of the biopsies.

Detection of gene doping
DNA
Vector
Protein
Effect
Proteomics

Many forms of genetic doping do not require the direct injection of genes in the desired target organ, i.e. the Epo gene may be injected into almost any site of the body to locally produce the Epo protein which will then enter the blood stream and stimulate the bone marrow. Finding the site of injection will be like looking for a needle in a hay stack. With injectable Epo use, close medical monitoring ensures that red blood cell parameters can be contained within set levels making it difficult to even be suspicious that illicit gene doping may have occurred.

The gene doping will in most instances result in the production of a human protein, which by itself is identical to the persons own proteins. Only the (blood) level of the protein may be indicative for doping abuse. In the case of Epo-type treatment, this might be detectable, because of the resulting increase in hemoglobin and hematocrit. However, genes may be turned on and off by taking specific medicines. Studies in monkeys have shown that Epo levels can be controlled in this way, resulting in desirable hematocrit levels [Ye et al., 1999].

According to Larry Bowers, the lead toxicology and testing expert with the US Anti-Doping Agency, there would be no way to test for gene doping with current technologies. The authors of a *Scientific American* article [Andersen et al., 2000] conclude their assessment by saying, '[F]or all intents and purposes, gene doping will be undetectable.' It may be impossible to detect the agents used in gene doping, but the effects can be measured.

A possible solution is the use of protein markers, as indicators for disruption of normal physiology. It will require the sampling and analysis of sets of proteins at the level of the individual athletes' physiology over time. With progress in proteomic techniques, which allows the simultaneous screening of hundreds of proteins, this technique may become valuable for anti-doping testing.

Research on the selection of protein markers best suited for this purpose should be started in order to introduce these assays as routine testing methods.

## 7 Preventive measures

### 7. 1 Regulations

Public authorities and sports organizations, including the International Olympic Committee, have condemned doping since the 1960s. The concerned substances were for the most part approved medicines from pharmaceutical companies. The recent advances in biological pharmaceuticals will have a great impact on the nature of medicines prescribed to patients but will also change the choice of performance enhancing medicines for athletes.

In the Netherlands, as well as other countries, clinical use of gene therapy is experimental. One needs permission from two offices which evaluate ethical issues (CCMO) and safety issues (COGEM). This guarantees that pharmaceutical grade vectors are used with known safety profiles. However the Genetically Modified Organisms Decree does not imply any restrictions on the availability of genetic materials. The only law limiting exchange of genetic materials is the Dutch decree on the export and import of strategic goods and the EC decree Nr. 3381/94 on the export control of goods, limiting import and or export of strategic goods, including genetic materials.

Gene therapy is only permitted in non-reproductive cells ensuring that gene therapy will not affect future generations.

The International Olympic Committee (IOC) has included the method of gene doping in their list of prohibited classes of substances and prohibited methods per January 1st, 2003.

Preventive measures for gene doping
Regulations
Detection
Education
Coordination

### 7. 2 Detection

The prohibition of gene doping by WADA and the international sports federations provides a strong basis for the elimination of gene doping in sports, but will depend on methods to determine the compliance of athletes with these regulations. As described above, detection of gene doping is very difficult. Gene therapy vectors may be measurable only shortly after administration and in many cases would require tissue sampling. The resulting protein is not different from the endogenously produced protein. It may only be possible to detect gene doping by repeated physiological protein profiling of athletes, allowing changes in protein levels to be perceived. These measurements need to be developed and evaluated in order to be introduced as routine testing methods. In addition, other preventive methods to minimize the use of gene doping in sports should be stimulated.



### 7. 3 Education

Most athletes will not have enough background knowledge to fully understand the potential health hazards imposed by gene doping. Therefore, it is of utmost importance that athletes and their supporting staff will be educated on this subject in order to prevent the use of gene doping. Athletes will receive information on the potential benefits of gene doping from the mass media such as newspapers, magazines and television. They will be tempted to try such a new therapy, especially when they are informed that such a form of doping may be almost impossible to detect. Athletes should be made aware of the risks involved in gene doping when used in an uncontrolled athletic setting without compromising the great possibilities that gene therapy offers for the treatment of certain illnesses. Risks that may involve themselves, their relatives and even the environment. Elite athletes and athletes in gyms appear to be the primary target groups.

### 7. 4 Coordination

In order to develop an effective strategy for the prevention of gene doping, national as well as international coordination is required. The inclusion of gene doping as a prohibited method on the doping list is only a first step. In this regard, the WADA should play a leading role. Coordination is necessary to set-up an educational programme for athletes and their supporting staff, as well as the general public. Also, research needs to be coordinated in order to investigate the development of methods to detect gene doping. The pharmaceutical industry should preferably subscribe to a code in which they state that they will not produce or sell genetic products for other than therapeutic use, banning gene doping.

On a national level, in the Netherlands, these activities may be coordinated by NECEDO, Nefarma (pharmaceutical industry) and NVGT (Dutch Society for Gene Therapy).

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## 8 Survey on gene doping

People from different disciplines in science and sports (appendix III) were interviewed in order to obtain an idea of the notion and possible impact of gene doping.

From the answers it is clear that people outside of the scientific community or pharmaceutical industry involved in gene therapy have little to no knowledge about the use of gene therapy. A general fear is that it may affect offspring and could cause cancer. They feel that detection of gene doping will be complicated and preventive measures will be difficult. On the other hand, they insist that gene doping will be used by athletes, at the time it will be available, which according to them will be in the coming years.

The professionals surrounding elite athletes are quite aware of the possibilities for gene doping. They think it may be used within a few years and that detection of gene doping will be very hard. They recommend the education of athletes, as well as their medical staff. In addition, they advocate the development of assays for gene doping measurement, such as physiological protein profiling in blood.

The pharmaceutical industry is well aware of the possibilities and risks of gene doping. Although gene therapy is an experimental treatment that needs further development, they foresee that gene doping will be used by (elite) athletes in the next years. They will not allow the use of their products outside prescribed use, including the use to enhance athletic performance. They see the detection of gene doping as a major problem and are willing to collaborate on the development of assays to detect the gene products from their medicines.

## 9 Conclusions

The athletic world will sooner or later be faced with the phenomenon of gene doping to improve athletic performance. The exact number of years that it will take for this method to enter the athletic arena is difficult to estimate, but it is most likely that this will happen within five years. Many genes that potentially have an effect on athletic performance are readily available. These genes are evaluated in clinical trials for the treatment of illnesses. The gene therapy vectors used in these studies may find their way to athletes and their supporting staff. Alternatively, illegal laboratories may be set-up to produce gene transfer vectors. In both instances, it seems unlikely that fail-safe detection methods will be developed. The uncontrolled use of non-therapeutic gene therapy by athletes imposes potential risks for both the user and the general public. It is questionable whether the existing regulations on genetic materials are sufficient to tackle such uncontrolled use. At this moment, a combination of developing a detection method based on proteomics and a clear education programme on the associated risks seems to be the most promising preventive method to counteract the possible application of gene doping.

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## 10 Recommendations

### 1) Promote the development of detection methods at a global scale

It is unlikely that a detection method for gene doping will be developed within the upcoming years. Methods either require invasive methods and show limited possibilities in itself or can only be realized through the full commitment of many parties. Current developments with proteomic techniques might provide a good basis for the development of a fail safe detection method. The scientific community should investigate and explore (new) possibilities for detection, preferably at a global scale. The World Anti-Doping Agency (WADA) would be the primary body to coordinate such an effort. Until a detection method for gene doping is developed the monitoring of athletes through regular blood sampling might provide an opportunity to screen for abnormal disruptions of the normal physiology – disruptions that might stem from gene doping. For this purpose existing monitoring methods, such as currently applied by the International Skating Union (ISU) and International Cycling Union (UCI), might be useful but perhaps new monitoring programmes are necessary.

### 2) Closely inform athletes on the potential consequences of gene doping

The consequences of the misuse of genetic therapies for the purpose of sport enhancement can be severe up to life threatening. In an effort to be the best, athletes will push their boundaries. Some athletes even turn to doping and in a worst case scenario turn to alternatively produced doping (like THG) or experimental medication (like RSR-13). To prevent gene doping from becoming the doping of choice for these athletes, clear information for athletes and their supporting staff on its severe health consequences is needed. Elite athletes and athletes in gyms appear to be the primary target groups.

### 3) Evaluate current regulations on genetic materials from a doping perspective

The clinical use of gene therapy is strictly regulated in the Netherlands through the Genetically Modified Organisms Decree based on two European directives. However, the clinical application of gene therapy might differ in many ways from its application for doping purposes. For instance, gene therapy for doping purposes might be applied outside the regular clinical setting with the involvement of illegal laboratories. These differences justify taking a closer look at the current regulations on genetic materials.

# Appendices

## Appendix I Abbreviations

CCMO	Central Committee on Research Involving Human Subjects
COGEM	Committee on Genetic Modification
Epo	Erythropoietin
IGF-I	Insulin-like growth factor-1
IOC	International Olympic Committee
NECEDO	Netherlands Centre for Doping affairs
NVGT	Dutch Society for Gene Therapy
VEGF	Vascular endothelial growth factor
WADA	World Anti-Doping Agency

## Appendix II Expert meeting

Participants Expert meeting 'Genetics & Doping'

October 1, 2003

Ministry of Health, Welfare, and Sport, The Hague, The Netherlands.

Prof.Dr. J.J.M. Marx, University of Utrecht (chair)

Prof.Dr. H.J. Haisma, University of Groningen

Dr. A.J. van der Lely, Erasmus Medical Centre Rotterdam

Dr. W.R. Gerritsen, Vrije Universiteit, Amsterdam

Prof.Dr. R.C. Hoeben, Leiden University Medical Centre

Dr. A.G. Vulto, Erasmus Medical Centre, Rotterdam

Dr. R.A. Tio, University of Groningen

Dr. E. van Breda, Maastricht University

Dr. O. Rabin, World Anti-Doping Agency

Dr. P. Schjerling, Copenhagen Muscle Research Center

Mr. P. de Klerk, Ministry of Health, Welfare and Sport

Mr. R. van Kleij, Netherlands Centre for Doping affairs

Mr. O. de Hon, Netherlands Centre for Doping affairs

After the meeting, Mrs. C. Ross-van Dorp, Minister of Sport, and members of the Dutch Parliament were informed.

## Appendix III Questionnaire

People that responded to the questionnaire used for the survey:

Sports physician Tjeerd de Vries  
Sports physician Fred Hartgens  
Sports physician Valentijn Rutgers  
Pharmacist Koos Brouwers  
Athlete Carl Verheijen  
Athlete Deborah Gravenstijn  
Athlete Gert-Jan Liefers  
Athlete Kasper Engel  
Scientist Theodore Friedman (American Society of Gene Therapy)  
Scientist Olivier Rabin (WADA)  
Company AMGEN (Jan van de Brand, CEO)  
Company Amsterdam Molecular Therapeutics (Jan Boesen, CEO)  
Company Crucell (Dinko Valerio, CEO)

### Questionnaire

1. Are you familiar with the term gene doping? What do you think it means?
2. Do you think gene doping will improve athletic performance? Will it be different from current doping strategies?
3. What, to your opinion, are the health risks of gene doping?
4. Do you think gene doping is used at this time or will be used in the near future? (if yes, could you give an estimated time frame?)
5. Do you think gene doping will be easily detectible?
6. Would it be possible to take preventive measures for gene doping?
7. Do you know athletes that have used doping and do you think they will use gene doping if this becomes available?
8. Would you be interested to know how gene doping works, and how would you try to get this information?
9. Do you think that sports physicians have enough knowledge about gene doping?
10. Do you think that people who use gene doping will have life-long effects of this treatment and will affect their children?

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### Internet sites

- CCMO: [www.ccmo.nl](http://www.ccmo.nl)
- COGEM: [www.cogem.nl](http://www.cogem.nl)
- IOC: [www.olympic.org](http://www.olympic.org)
- WADA: [www.wada-ama.org](http://www.wada-ama.org) and [Wada stage.wada.netcomsus.com](http://Wada.stage.wada.netcomsus.com)
- NECEDO: [www.necedo.nl](http://www.necedo.nl)





The Netherlands Centre for Doping affairs (NeCeDo) is the national anti-doping agency in the Netherlands with a primary responsibility for: information services, policy advisory, development of regulations, education, and the conduct and coordination of research.

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