Der Standpunkt der Welt-Anti-Doping-Agentur (WADA) zur Genmanipulation im Sport

R. Klaus Müller

Wenn in den Medien „Gen-Doping“ schon seit längerem als düstere Prognose für die nächste Zukunft erscheint, dann geschieht das unter einem unklaren Begriff. Denkbare Kategorien genetischer Manipulationen zur Leistungssteigerung im Sport sind die, die in Abbildung 1 aufgeführt sind, und gewöhnlich unzutreffend unter „Gen-Doping“ subsummiert werden.

A	**Gentechnische Herstellung von Arznei- bzw. Dopingmitteln anstelle deren Gewinnung aus Organen oder Geweben**
B	**Genmanipulation an Organen/Geweben des (erwachsenen) Menschen**
C	**pränatale Genveränderungen (am Genom, der „Keimbahn“)**
	- zum Erreichen (oder der Verhinderung) bestimmter Individualeigenschaften
	- zum „Klonen“

Abb. 1

Die gentechnische Herstellung von Arzneimitteln wie Erythropoietin (EPO), Insulin oder Wachstumshormon hGH ist seit langem zunehmend üblich. Sie führt natürlich auch zum Missbrauch im Sport ebenso wie bei anderen Dopingmitteln, ist aber keine neue Herausforderung, sondern ermöglicht sogar die analytische Untersuchung von nicht absolut identischen körpereigenen Hormonen.

Pränatale Manipulationen am Genom, an der Keimbahn, die auf die Züchtung neuer „optimierter“ Individuen oder auch auf das Klonen (die Züchtung identischer Lebewesen) hinauslaufen, sind nach übereinstimmenden Expertenmeinungen „science fiction“ und werden das – auch angesichts der gesetzlichen Regelungen hierfür – bleiben.

Keineswegs irreal sind dagegen – obwohl vorerst noch im tierexperimentellen Stadium – genetische Manipulationen an somatischen Zellen oder Geweben. Auf sie richten sich weltweite Forschungen mit dem Ziel der Gentherapie von Krankheiten, die auf genetische Abweichungen oder Schäden zurückgehen.

Die Beeinflussung der Genfunktion auf somatischer Ebene kann auf verschiedenen Wegen erfolgen, die im folgenden Schema umrissen sind.

Gentransfer in vivo: Einführung von Nukleinsäuren
DNA- oder **RNA**- Transfer in Zellen
ex vivo: Einbringen genveränderter Zellen in lebende Gewebe
Der Transfer der Nukleinsäuren in Zellen erfolgt über **Vektoren**: ***Viren***, in deren Genom diese vorher eingebaut wurden, über ***Liposomen*** oder z.B. über ***Elektroporation.***

Beeinflussung der
Genexpression (der Aktivität des Gens, der Produktion eines Proteins über die Kette)
DNA im Zellkern – messenger-RNA in das Plasma,
t-RNA zur Peptidkettenbildung aus Aminosäuren

Stimulation
- durch Initiatorgene („Anschalten")
- durch Promotoren
- durch Blockade regulierender Rezeptoren

Repression – invers zur Stimulation

Ziel der hierauf gerichteten Forschung ist die **Gentherapie**, die Behandlung auf genetische Abweichungen zurückgehender Krankheiten.

Abb. 2 Varianten der somatischen Genmanipulation (der Genbeeinflussung im lebenden Organismus)

Das Komitee Gesundheit, Medizin und Forschung (Health, Medical and Research = HMR) der Welt-Anti-Doping-Agentur (WADA) und dessen Subkomitee für die Doping-Liste waren bereits bei ihrer Konstituierung im Jahre 2000 überzeugt, dass denkbare genetische Manipulationen schon jetzt in das Doping-Verbot eingeschlossen werden müssen.

Um eine allseits akzeptable Definition vorzubereiten und nach Möglichkeit bereits vor künftig auftretendem Missbrauch gentherapeutischer Techniken Nachweisverfahren anzudenken, wurde daher ein internationales Symposium mit namhaften Experten der gentherapeutischen und molekulargenetischen Forschung vorbereitet. Ursprünglich für Ende September 2001 in New York geplant, fand die Konferenz letztlich im März 2002 unter dem Titel „Genetic enhancement of athletic performance" statt. Veranstaltungsort war das Banbury Center (Long Island, NY) des berühmten Cold Spring Harbour Laboratory, in dem mehrere Nobelpreisträger ihre molekulargenetischen Arbeiten durchgeführt haben.

Das erklärte Ziel bestand in der Erkundung des Standes der Forschung und Technologie, der Ethik und der rechtlichen Aspekte des Gentransfers. In der Überzeugung, dass die Betrüger im Sport von heute wahrscheinlich auch nach Wegen des Missbrauchs der Gene-

tik für morgen suchen werden, sieht sich die WADA aufgerufen, dem möglichen Missbrauch des Gentransfers im Sport entgegenzuwirken.

Dazu wurde auch die „Doping-Liste“ verbotener Substanzen und Methoden um diese neue Kategorie erweitert, die sowohl für Kontrollen im Wettbewerb als auch außerhalb des Wettbewerbs (Trainingskontrollen) gelten soll:

> **Gene or cell doping is defined as the unapproved use of genes, genetic elements and/or cells that have the capacity to enhance athletic performance.**

Gen- oder Zell-Doping ist definiert als die nicht (medizinisch) begründete Anwendung von Genen, genetischen Elementen und/oder Zellen, die die Fähigkeit zur Leistungssteigerung von Athleten aufweisen.

Folgende Vorträge wurden gehalten (Kurzform):

- The history of the nature of doping (*G.I. Wadler, New York*)
- Current methods of screening (*R.K. Müller, Leipzig*)
- Principles of gene therapy - history, current state and directions (*T. Friedmann, San Diego*)
- Target tissues, muscle (*H.L. Sweeney, Philadelphia*)
- Metabolism of exercising muscle (*C. Sundberg, Stockholm*)
- Detection of gene transfer and genetic approaches to pain control... (*J. Glorioso, Pittsburgh*)
- Stem cells, injury and tissue repair (*C. Evans, Boston*)
- Mitochondrial energy production and performance (*D.C. Wallace, Atlanta*)
- EPO (*B.J. Byrne, Gainesville*)
- IGF-1 (*G. Goldspink, London*)
- Metabolic changes - microarrays (*J. Glorioso, Pittsburgh*)
- Regulatory issues (*A.P. Patterson, Bethesda, und O. Haguenauer, Paris*)
- Legal, medical perspective (*B.-M. Knoppers, Montreal*)
- Biomedical ethics of enhancement (*E.T. Juengst, Cleveland*)
- The ethics of sport (*A. Schneider, London*)
- Sport and the law (*R.R. Young, Colorado Springs*)

Obwohl zahlreiche gentherapeutische Forschungsrichtungen verfolgt werden, scheint die Steigerung der körpereigenen Erythropoietin-Produktion bereits am weitesten gediehen und einer klinischen Anwendung – damit aber auch dem Missbrauch – am nächsten zu sein (Beispiel siehe Abbildung 3).

Efficient and regulated erythropoietin production by naked DNA injection and muscle electroporation

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Communicated by C. Thomas Caskey, Merck & Co., Inc., West Point, PA, March 24, 1999 (received for review December 8, 1998)

ABSTRACT We show that an electric treatment in the form of high-frequency, low-voltage electric pulses can increase more than 100-fold the production and secretion of a recombinant protein from mouse skeletal muscle. Therapeutical erythopoietin (EPO) levels were achieved in mice with a single injection of as little as 1 μg of plasmid DNA, and the increase in hematocrit after EPO production was stable and long-lasting. Pharmacological regulation through a tetracycline-inducible promoter allowed regulation of serum EPO and hematocrit levels. Tissue damage after stimulation was transient. The method described thus provides a potentially safe and low-cost treatment for serum protein deficiencies.

1: Hum Gene Ther 2001 May 20;12(8):871-81

In vivo gene transfer in mouse skeletal muscle mediated by baculovirus vectors.

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Baculovirus vectors are efficient tools for gene transfer into mammalian cells in vitro. However, in vivo gene delivery by systemic administration is hindered by the vector inactivation mediated by the complement system. To characterize further the gene transfer efficacy of baculovirus we examined the vector transduction efficiency in skeletal muscle. Vectors expressing vesicular stomatitis virus glycoprotein (VSV-G) in the viral envelope were generated by inserting the VSV-G coding sequence downstream of the polyhedrin promoter. Two viruses were constructed to carry either the Escherichia coli beta-galactosidase (beta-Gal) gene or the mouse erythropoietin (EPO) cDNA cloned downstream of the cytomegalovirus immediate-early promoter and enhancer. The greater gene transduction efficiency of the Bac-G-betaGal vector was confirmed by comparing the beta-Gal expression level in a variety of human and mouse cell lines with that obtained on infection with Bac-betaGal, a vector that lacks VSV-G. Similarly, a 5- to 10-fold increase in beta-Gal expression between Bac-G-betaGal and Bac-betaGal was observed when mouse myoblasts and myotubes were infected. The same increase in beta-Gal expression was detected on injection of the Bac-G-betaGal vector in the quadriceps of BALB/c and C57BL/6 mice. In contrast, a 2-fold difference in transduction was observed between these two vectors in DBA/2J mouse strain. Last, expression of EPO cDNA was detected for at least 178 days in DBA/2J mice on Bac-G-EPO injection into the quadriceps whereas EPO expression declined to normal values by 35 days postinfection in BALB/c and C57BL/6 mice. Thus, these results indicate that baculovirus may be considered a useful vector for gene transfer in mouse skeletal muscle and that persistence of expression may depend on the mouse strain used.

Abb. 3

Im abschließenden Statement gab es eine bemerkenswerte Übereinstimmung hinsichtlich

- des möglichen Nutzens gentechnischer Entwicklungen für die menschliche Gesellschaft;
- der Notwendigkeit eines geeigneten sozial/rechtlichen Rahmens für diese Forschungen
- und der ethischen Erfordernis, Missbrauch dieser Forschungsergebnisse zu verhindern.

Daraus ergab sich die erklärte Absicht, den Informationsaustausch zwischen Forschern der Molekulargenetik und Gentherapie sowie der WADA künftig fortzusetzen. Das begründet die Hoffnung, rechtzeitig Ansätze zum Nachweis genetischer Manipulationen im Sport im Sinne einer Vorwärtsverteidigung zu finden.

Das Komitee HMR der WADA hält mit seiner Ausschreibung von Forschungsrahmenthemen auch dafür ausdrücklich Fördermittel bereit.

Im abschließenden Statement (siehe Anhang) appelliert die WADA an alle Verantwortlichkeitsebenen für einen fairen Sport, gegen diese neue Gefahr eines drohenden Missbrauchs wissenschaftlichen Fortschritts aufzutreten.

Anhang

WADA Conference Sheds Light On The Potential Of Gene Doping

New York - A combination of regulation, education, and research is the best current method for addressing the prospect of gene doping in sport from becoming a reality, the World Anti-Doping Agency (WADA) reported today following its two-and-one-half day conference on *Genetic Enhancement of Athletic Performance.*

The conference, held at the Banbury Center of the Cold Spring Harbor Laboratory on Long Island from March 18 to 20, brought together international experts and leaders in biology and genetics, sports medicine, policy makers, legal experts, representatives of the Olympic Movement and athletes to explore the science, technology, and ethical issues facing the sports community as a consequence of gene transfer technology.

"Gene therapy has enormous potential to revolutionize medicine's approach to curing disease and improving the quality of life. Unfortunately, this same technology, like many others, can be abused to enhance athletic performance," said WADA Chairman Richard W. Pound.

"WADA is committed to confronting the possible misuse of gene transfer technology in sport. The same kinds of people who cheat in sport today will probably try to find ways to misuse genetics tomorrow. WADA is grateful to all those who helped us gain an understanding of this new field so we can consider how best to respond to the possible misuses.

"We found a remarkable degree of confluence amongst the scientific and sport representatives regarding the possibilities of benefit to the community at large from developments in genetic therapy, the need for a properly considered social framework for such activities, and the need to prevent the misuse of this developing branch of science."

"We must underscore that the work on genetic therapies should be considered research, promising for the future betterment of mankind but still unpredictable and of unproven safety," said Ted Friedmann, professor of Pediatrics at the University of California San Diego, Center for Molecular Genetics. "The time is right, however, for the sport and science communities to begin working out how to prevent the possible misuse of these methods in the future."

The conference participants came to a series of conclusions, some general and others specific to sport:

I. General

A. Gene transfer technology, which is still at the investigational stage, is nevertheless already beginning to demonstrate clinical efficacy.

B. While genetic technologies hold immense therapeutic promise, there is potential for their misuse, including attempts at the enhancement of athletic performance.

C. The collective efforts of scientists, ethicists, athletes, sports authorities, medical practitioners, professional societies, pharmaceutical and biotech industries, and public authorities (including governments) will be required to avert such misuse.

D. The compliance with established international standards pertaining to genetic experimentation involving human subjects, such as the Helsinki, Geneva, and Inuyama Declarations, that prevent unethical research is essential. The application of genetic transfer technologies should be consistent with established standards of professional behavior.

E. The pace of research in the field of genetic transfer technology is such that governmental and other regulatory agencies must work with a continued sense of urgency to establish a social and policy framework to guide this research and its applications and sanction breaches of the framework.

F. Broad public discussion and the development of social and policy frameworks must surround the distinction between genetic therapy and genetic enhancement. The time for the social framework to be established is before abuses occur, not after-the-fact.

II. Sport Specific

A. Athletes, in common with other people in society, are entitled to the benefits of genuine therapeutic applications to treat injuries and other medical conditions.

B. There are evident risks that genetic transfer technologies might be used in a manner that would be contrary to the spirit of sport or potentially dangerous to the health of athletes. Akin to doping in the present generation, genetic transfer technology that is non-therapeutic and merely performance-enhancing should be prohibited.

C. The definition of doping used by WADA, the IOC, international sports federations (IFs), and national authorities should be expanded to include the unapproved use of genetic transfer technologies.

D. One of the benefits of genetic technology is its potential use in the detection of prohibited substances and methods.

E. The scientific community has recognized the need for the continued development and refinement of methods that will permit the detection of the misuse of genetic transfer technologies in sport. The conference noted there are a number of approaches that currently exist, or are in development, that will permit such detection.

F. The present focus of WADA's research grants toward the study of the detection methods for the misuse of oxygen carrying agents and growth factors should be extended to include the detection of genetic transfer technologies and their effects.

G.The World Anti-Doping Code, that is planned for implementation by 2004, should include language prohibiting the use of genetic transfer technologies to enhance athletic performance.

H. WADA calls upon its government members, in particular, to expedite the development of a global social framework for the application of genetic transfer technologies that address the potential misuse of these technologies in sport and a publicly stated deadline for the adoption of that framework.

I. WADA calls upon governments to consider the following recommendations for inclusion in the regulatory framework pertaining to genetic transfer technologies and related research:

1. address breaches of the social framework within the criminal or penal realm
2. extend corporate liability to directors, officers and senior employees
3. extend civil and criminal limitation periods in respect of breaches of the regulatory framework
4. require detailed record-keeping in respect of all applications of gene transfer technologies with independent audit requirements
5. expand standards of medical and professional behavior to prohibit the improper use of genetic transfer technologies and that such rules be actively enforced

J. WADA calls upon governments and the sports movement to establish and fund educational and ethics programs designed to prevent the possible misuses of genetic transfer technologies in sport. WADA is willing to coordinate the design and dissemination of such programs.

K. WADA and the scientific community will establish a mechanism for continuing dialogue and consultation around the subject of genetic transfer technologies.

The following participated in the conference:

Bowers, Larry:U.S. Anti-Doping Agency

Breivik, Gunnar:Norwegian University of Sport & Physical Education

Byrne, Barry:University of Florida School of Medicine

Cohen-Haguenauer, Odile:Saint-Louis Hospital, Paris, France

De Rose, Eduardo H.:Pan-American Sports Organization

Drinkwater, Barbara:Research Physiologist, retired, Pacific Medical Center, Seattle

Evans, Christopher:Center for Molecular Orthopedics, Harvard Medical School

Fitch, Ken :Chairman, Medical Advisory Committee, Australian Sports Drug Agency

Friedmann, Theodore:Center for Molecular Genetics, University of California, San Diego; member, WADA Health, Medical, and Research Committee

Garnier, Alain:Chairman of the Monitoring Group of the Anti-Doping Convention, Council of Europe. WADA Medical Consultant

Glorioso, Joseph:Director of the Pittsburgh Molecular Medicine Institute, University of Pittsburgh. President elect of the American Society of Gene Therapy

Goldspink, Geoffrey:Division of Basic Biomedical Sciences, Royal Free & University College Medical School

Graf-Baumann, Toni:FIFA Sports Medical Committee; Chairman, FIFA Doping Control Subcommittee

Juengst, Eric:Center for Biomedical Ethics, Case Western Reserve University, Cleveland

Knoppers, Bartha-Maria:Center for Public Law, Université de Montréal

Koss, Johann:WADA Health, Medical & Research Committee
Ljungqvist, Arne:Chairman, WADA Health, Medical & Research Committee; vice president, IAAF

Mbanya, Jean-Claude:Endocrine & Diabetes Unit, University of Yaoundé 1, Cameroon

Mueller, Klaus:Forensic Toxicology, Leipzig University; Institute of Doping Analysis Dresden-Kreischa, Germany

Pipe, Andrew:Canadian Centre for Ethics in Sport & University of Ottawa Heart Institute

Pound, Richard W.:Chairman, World Anti-Doping Agency

Riding, Michael:Medical Commission International Paralympic Committee

Schneider, Angela:Faculty of Health Sciences, The University of Western Ontario. WADA Director, Ethics and Education

Segura, Jordi:IOC Medical Commission

Shobe, Joel:Medical Advisor, International Skating Union

Steinacker, Juergen:Dept. Sport and Rehabilitation Medicine, Ulm University, Germany; International Rowing Federation

Sundberg, Carl:Dept. of Physiology & Pharmacology, Karolinska Institutet, Stockholm, Sweden

Sweeney, H. Lee:Dept. of Physiology, University of Pennsylvania

Verbiest, Philippe:Lawyer, UCI Legal Advisor

Wadler, Gary :NYU School of Medicine; Medical Advisor, Office of National Drug Control Policy;member, WADA Health, Medical, and Research Committee

Wallace, Douglas:Emory University School of Medicine, Atlanta

Young, Richard:Lawyer, Holme Roberts & Owen LLP

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