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Office of Technology Assessment at the German Parliament

TAB- Project „Gene doping“

Documentation of principal findings

OFFICE OF TECHNOLOGY ASSESSMENT
AT THE GERMAN PARLIAMENT

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Foreword

Scientific and medical progress is leading to ever more advanced molecular biological techniques and to improved knowledge of how genes and cells function. Development of new substances and techniques is likely to lead to the emergence of qualitatively new forms of doping. As increasingly complex techniques for influencing the activity of genes with the aim of enhancing physical performance are developed, it will become ever more difficult to prove that such prohibited doping techniques have been used.

These developments will pose a particular challenge to the systems of testing and sanctions applied by sporting bodies and to national legislation that makes doping in sport a criminal activity. Though the precise pattern of a possible proliferation of gene doping is still unclear, it is imperative that the problem be addressed without delay.

In view of what a highly charged topic this is proving to be, the permanent committees of the German Bundestag decided to look into the question of gene doping. For its part, the Sports Committee instructed the Office of Technology Assessment at the German Parliament (TAB) to undertake an investigation into the topic of gene doping. In response to a decision by the Committee for Education, Research and Technology Assessment, which is responsible for the TAB, the TAB performed a project on gene doping. The content of this is now complete and the final report is expected to be released in March of this year.

The present report documents the principal findings of the TAB project on gene doping and invites discussion of these findings.

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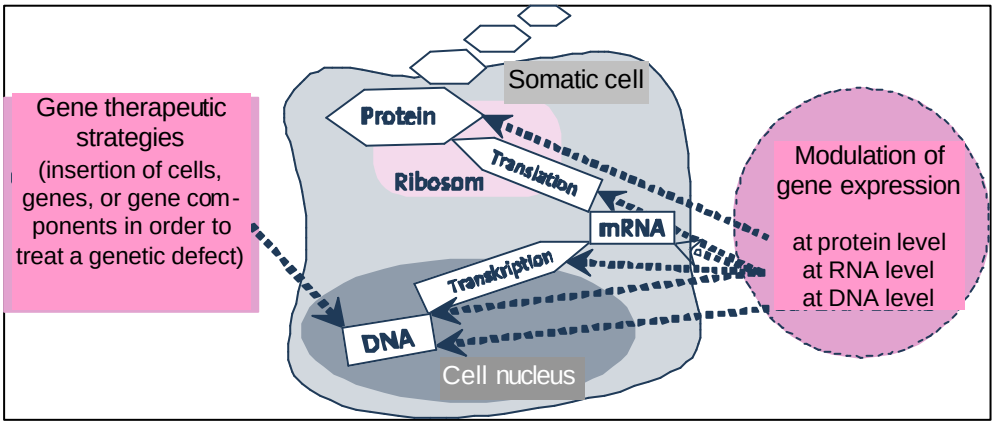
1. WHAT, PRECISELY, IS GENE DOPING?

The term *gene doping*, the object of investigation in the TAB project, is often construed very narrowly, namely as the misuse of techniques of gene therapy and cell therapy. However, this narrow focus excludes a number of potentially important scientific and medical developments that are relevant to future doping practice.

GENE DOPING – IN THE NARROW AND THE BROAD SENSE

The analysis undertaken by the TAB is therefore not limited to gene doping in the narrow sense of misuse of techniques of gene therapy and cell therapy in which genetic material in the form of DNA or RNA is inserted into a cell, an organ, or an organism. Instead, the TAB based its investigation on the broader interpretation adopted by the World Anti-Doping Agency (WADA), which explicitly defines gene doping to include the influencing of gene activity by other methods: "non-therapeutic use of cells, genes, genetic elements, or of the modulation of gene expression, having the capacity to improve athletic performance".

FIG. 1 POSSIBLE FOUNDATIONS FOR GENE DOPING: GENE THERAPY AND MODULATION OF GENE EXPRESSION



Source: illustration by authors

Only by adopting this broader interpretation is it possible to include all relevant methods, techniques, and agents in the assessment. The scientific basis of the new possibilities for (gene) doping is formed by the ever-advancing techniques of molecular biology and increasing knowledge of the molecular mechanisms of cell function. The social and political explosiveness of the topic arises from the fact that these advances will

dramatically increase the possibilities for manipulating gene activity in specific and subtle ways that are likely to be increasingly difficult to detect. Whether this process of manipulation occurs by transmission of actual genetic material, i.e. DNA or RNA, or by some other pharmacologic mechanism is largely irrelevant for the purposes of an assessment of consequences or research aimed at prevention.

In the present report the term "gene doping in the narrow sense" is used when only methods based on gene therapy or cell therapy are being referred to. Otherwise, the term "gene doping" is understood to mean gene doping in the broader sense as defined by the WADA.

WHAT GENE DOPING IS NOT

According to a widely held notion, gene doping is aimed at "improving" the genetic equipment of athletes. This belief is based on the assumption that research into the human genome must have resulted in extensive knowledge of gene variants that bring about extraordinary physical capabilities. According to this idea, techniques of gene therapy and/or stem cell therapy could in the future be used to transfer such "high performance variants" to an individual – either at the embryonic stage or during childhood or even adulthood – in such a way as to replace that individual's lower-performance gene variants. Other "options" that could arise in this scenario include forms of prenatal or preimplantation diagnosis in which the "selection parameters" would be genetic factors for particular physical or mental abilities.

However, a detailed analysis of the results of genome analysis shows that molecular genetic knowledge of "high performance gene variants" is still extremely limited, imprecise, and contradictory, with the result that "promising" techniques for inducing specific alterations in an individual's genetic disposition are extremely unlikely to be developed in the foreseeable future. Accordingly, the TAB project has uncovered *absolutely no evidence* that any strategies based on human selection or breeding for enhanced sporting ability are likely to become technically feasible within the foreseeable future. At present, therefore, ideas about the possibility of gene doping in this narrow sense have no scientific basis.

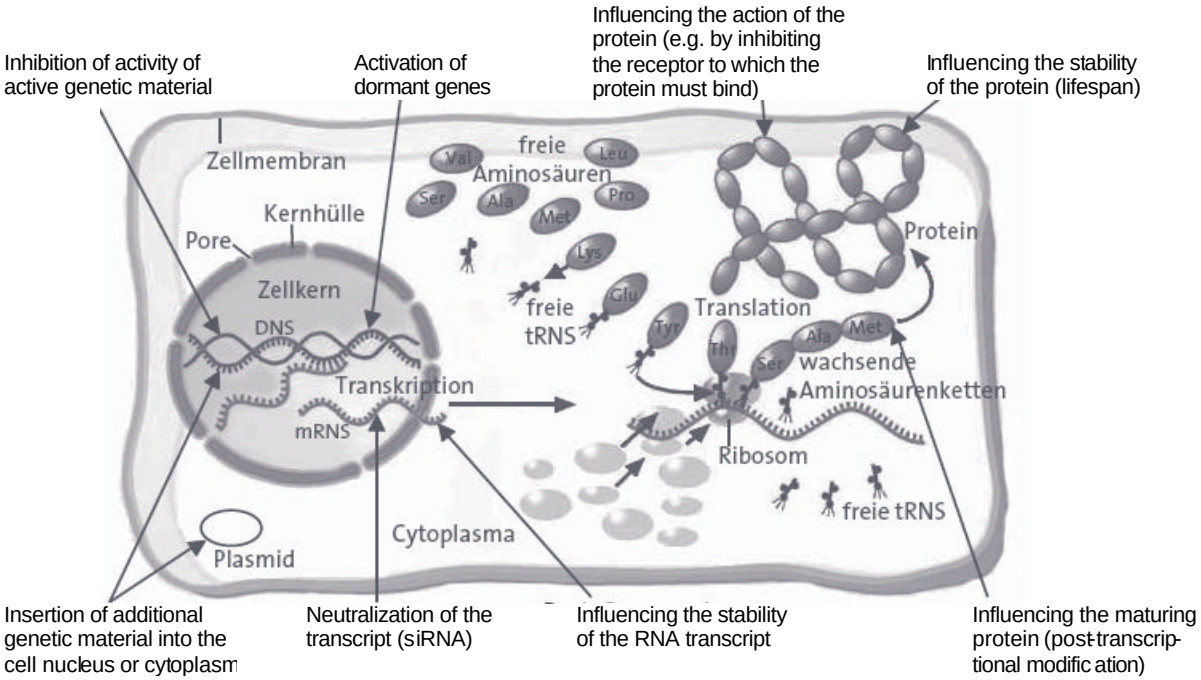
GENE REGULATION – THE STARTING POINT FOR GENE DOPING

The objective of gene doping is therefore to specifically influence (modify) the activities of the body's genes by activating them or by strengthening, weakening, or blocking their action.

"Coding" genes exert their action when they are "expressed", i.e. when the information that they contain is "read" and the cell thereupon produces a functionally active protein. In the first step in this process the segment of the nuclear DNA that codes for the

protein concerned is copied, not in the form of DNA, but in slightly altered chemical form as RNA. The product of this process of *transcription* is known as *messenger RNA* (mRNA). In a complex process known as *translation*, mRNA serves as a template for the production of an absolutely specific protein. The body's mechanisms for controlling and influencing this gene expression are known as *gene regulation*.

FIG. 2 METHODS OF MODIFYING THE BODY'S GENE ACTIVITY



(*Zellmembran* = cell membrane; *Kernhülle* = nuclear envelope; *Zellkern* = cell nucleus; *DNS* = DNA; *Transkription* = transcription; *mRNS* = mRNA; Cytoplasma = cytoplasm; *freie Aminosäuren* = free amino acids; *freie tRNS* = free tRNA; *wachsende Aminosäurenketten* = growing amino acid chains; *Ribosom* = ribosome)

Source: P. Diel, from an illustration by Hoffmann-La Roche Ltd.

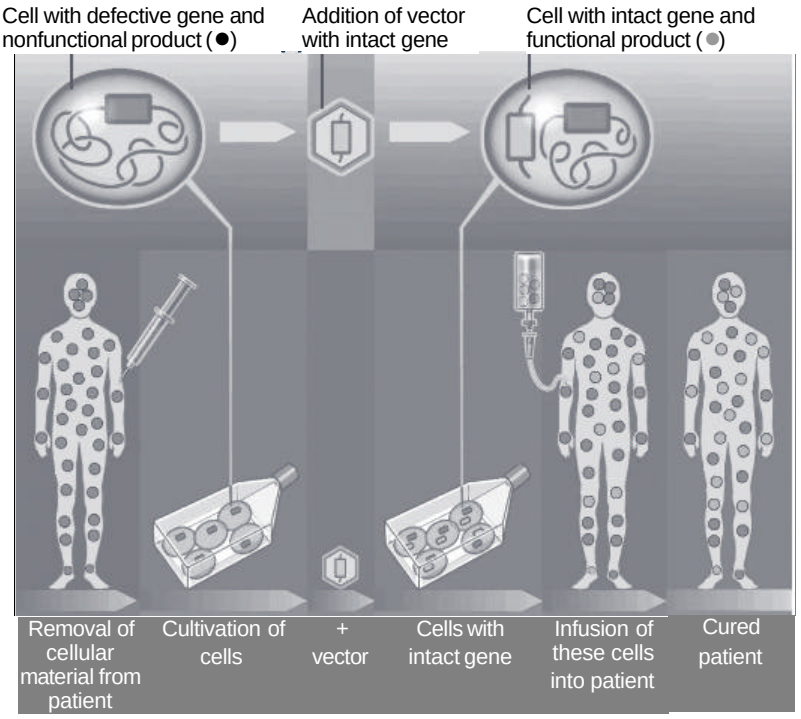
Since each and every step in gene expression is subject to highly complex physiological regulatory mechanisms, there are many points at which pharmacologic or molecular biological modulation is potentially possible – either for therapeutic intervention or for doping purposes.

GENE THERAPY

When a gene fails to fulfill its normal function in a cell, tissue, or organ and this circumstance gives rise to a disease, a *genetic defect* is said to exist. Such a genetic defect may either have been inherited or have arisen in the course of the individual's life. The

term *gene therapy* refers to strategies in which genes or genetic elements are introduced into cells from without in order to remedy genetic disorders.

FIG. 3 PRINCIPLE OF GENE THERAPY



Source: Bibliographisches Institut & F.A. Brockhaus

The process of introducing genes into cells is known as *gene transfer*. In most cases this is achieved by means of a *vector* ("carrier"; most of the vectors that have been used to date are specially modified viruses) that bears the required therapeutic genetic element. Gene therapy is intended to enable the body to, as it were, produce its own medicine. Notwithstanding common statements to the contrary, the change induced in this way is in many cases not permanent, but rather a transitory change that may need to be reinduced.

To date, successful attempts at gene therapy in human beings have been limited to techniques based on gene *addition* and gene *inactivation*. Only in animal experiments have techniques based on gene *correction*, gene *replacement*, and gene *activation* been successful. The gene therapies that have been tested in humans to date have been directed mostly at cancers, monogenic hereditary diseases, infectious diseases (especially HIV infection), and cardiovascular disorders. However, the value of the therapeutic results that have been achieved to date using techniques of gene therapy is hotly disputed.

OTHER METHODS OF MODIFYING GENE ACTIVITY

In addition to the methods that are unambiguously described as constituting gene therapy, there exist many other modern pharmacologic strategies that are intended to induce a specific modification of the body's gene activity in order to achieve a desired therapeutic outcome. The pharmacologic agents concerned include a broad range of in some cases very complex biomolecules such as proteins and RNA, but also some simple compounds that are very easy to produce chemically, as seen from the examples given below.

In many cases it is scarcely possible to draw a sharp distinction between "conventional" methods and approaches based on gene therapy. This is another reason for adopting a broad definition of the term "gene doping".

2. WHAT IS GENE DOPING INTENDED TO ACHIEVE?

The most likely methods by which gene doping might be attempted relate to three areas of physiology and the molecular regulation thereof, namely formation of skeletal muscle, oxygen supply, and energy supply. No concrete evidence was found to support the many reports of pain sensitivity being influenced by means of gene doping.

POSSIBLE PHYSIOLOGICAL METHODS OF GENE DOPING

- *Oxygen supply:* hemoglobin concentration, blood vessel supply (molecular targets: EPO, HIF, VEGF)
- *Skeletal muscle:* growth, structure, strength, endurance, regeneration (molecular targets: myostatin, HGH/IGF/MGF, Pax7, PPAR-delta)
- *Energy supply:* fatty acid and glucose metabolism in the liver and muscles (molecular targets: FATPs, GLUTs, PTP-1B)

The following tables summarize some important examples of gene doping-relevant research initiatives and development projects that were identified in the TAB project. It is seen that of the techniques listed as being presently at the stage of clinical studies, only one (induction of expression of VEGF-2 in cardiac muscle by means of "naked" DNA) is/was an explicitly gene therapeutic method. The other techniques that have reached an advanced stage of development are based on pharmacologic methods of modifying gene activity. Success in the preclinical phase, i.e. in animal experiments, has been obtained with a large number of techniques that constitute gene doping in both the narrow (e.g. the well-known case of Repoxygen) and the broad sense.

TABLE 1 GENE DOPING TECHNIQUES: *MODULATION OF OXYGEN SUPPLY*

Molecular target	Intended therapeutic use (diseases)	Potential performance enhancement	Method/technique (*R&D stage*)
Increased number of red blood cells			
Erythropoietin (EPO)	Blood diseases, especially anemia in dialysis patients	Increased oxygen transport function of blood (known and established as a result of EPO use in endurance sports)	Increased production of EPO in muscle as a result of gene addition (*Repoxygen; animal experiments*) Stabilization of transcription factor HIF by means of small molecules leading to overexpression of EPO (*clinical study stopped because of possible side effect*)
Increased number of blood vessels in tissues (angiogenesis)			
Vascular endothelial growth factor (VEGF)	Ischemia (lack of blood supply) or destruction of blood vessels resulting from heart disease Cancer (angiogenesis *inhibitors* can be used to retard cancer growth)	Increased oxygen exchange capacity in tissues	Induction of expression of VEGF-2 in heart muscle by means of naked DNA (*clinical study showed no effect in phase II for primary indication; other indications planned.*)

Source: Compiled by the present authors on the basis of Diel, P., Friedel, U. (2007): Gendoping: Techniken, potenzielle biologische Ziele und Möglichkeiten des Nachweises [Gene doping: techniques, potential biological targets, and possibilities for detection]. Expert report commissioned by the German Bundestag, submitted to the Office of Technology Assessment at the German Parliament. German Sport University Cologne

TABLE 2 GENE DOPING TECHNIQUES: *STRUCTURE/PROPERTIES OF SKELETAL MUSCLE*

Molecular target	Intended therapeutic use (diseases)	Potential performance enhancement	Method/technique (*R&D stage*)
Muscle growth (increased mass)			
Myostatin (growth-limiting factor)	Hereditary and age-related muscular atrophy Possibly type 2 diabetes	Obvious potential for use particularly in strength-intensive sports; natural mutations known to occur in humans and, e.g., cattle	Inhibition of myostatin by: a) blockade of the myostatin gene (*animal experiment)* b) inhibition of myostatin synthesis by metalloproteinases (*animal experiment*) c) Blockade of the myostatin receptor (*clinical study*) d) Inhibition of myostatin itself by antibodies (*clinical study)*
Muscle metabolism and regeneration			
HGH (human growth hormone) in combination with IGF or MGF (muscle-specific variant)	Growth disorders, muscular atrophy	Increased strength and mass Lipid breakdown (anti-aging!)	Increased HGH and IGF production in muscle by gene addition (*animal experiment*)
Transcription factor Pax7 (influences muscle regulation factors)	(Regeneration after) injuries	Better regeneration	Pax7 blockade causes defect in muscle regeneration; (*animal experiment*)
Muscle composition: increased proportion of type I fibers (slow contraction, lipid combustion)			
Receptor protein PPAR-delta (induces transformation of muscle fibers)	Metabolic syndrome	Increased endurance, e.g. due to improved lipid utilization ("marathon mouse")	Overexpression of PPAR-delta by gene addition (*animal experiment*) Activation of PPAR-delta agonists (*drug screening*)

Source: Compiled by the present authors on the basis of Diel, P., Friedel, U. (2007): Gendoping: Techniken, potenzielle biologische Ziele und Möglichkeiten des Nachweises [Gene doping: techniques, potential biological targets, and possibilities for detection]. Expert report commissioned by the German Bundestag, submitted to the Office of Technology Assessment at the German Parliament. German Sport University Cologne

TABLE 3 GENE DOPING TECHNIQUES: *INFLUENCING OF ENERGY SUPPLY*

Molecular target	Intended therapeutic use (diseases)	Potential performance enhancement	Method/technique (*R&D stage*)
Increased rate of uptake of fatty acids into muscle			
Fatty acid transport proteins (FATP1, CD36)	Obesity	Increased endurance due to improved lipid utilization	Overexpression of fatty acid transport proteins by means of naked DNA (*animal experiment*)
Increased rate of release of glucose in the liver, increased rate of uptake of glucose into muscle			
Glucose transport proteins (GLUTs)	Diabetes	Increased performance due to better glucose utilization	Overexpression of GLUTs by gene addition (*animal experiment*)
Insulin receptor			Inhibition of the enzyme PTP-1B by means of siRNA leading to activation of the insulin receptor (*animal experiment*)

Source: Compiled by the present authors on the basis of Diel, P., Friedel, U. (2007): Gendoping: Techniken, potenzielle biologische Ziele und Möglichkeiten des Nachweises [Gene doping: techniques, potential biological targets, and possibilities for detection]. Expert report commissioned by the German Bundestag, submitted to the Office of Technology Assessment at the German Parliament. German Sport University Cologne

In order to obtain additional information on potentially relevant trends in the field of gene therapy in particular, the state of development of this field as a whole was also reviewed. This review showed that the number of gene therapy studies that have reached phase III (the phase of clinical trials in which a drug is tested for efficacy compared to established drugs and/or placebo) is still very small. Gene therapy is thus not an established form of medical treatment, but rather is still at the experimental stage in the vast majority of cases. To date the European Medicines Agency has received only one application for marketing authorization of a gene therapy product (for the treatment of an aggressive brain tumor), whereas in China a gene therapy product for the treatment of certain types of tumor has been licensed since 2003.

On the other hand, the year 2006 saw the performance of the first clinical studies for disease entities that are not life-threatening, but merely impair the affected person's quality of life. Notable also is the fact that in a high proportion of gene therapy approaches the object of study has been a tissue hormone (e.g. a growth factor). These are precisely the same molecules that constitute one of the most frequently abused categories of substance in "conventional" doping practice. Finally, it should be noted

that the proportion of gene therapy techniques that use naked DNA has risen continuously in the past few years. This is of importance in relation to possible gene doping insofar as the use of nonviral DNA is considerably simpler, and presumably also less risky, than the use of viral vectors.

3. SPREAD OF GENE DOPING – HOW, WHEN, WHERE

Ready availability of methods and agents that are by their nature suitable for gene doping is a necessary prerequisite for gene doping. A consideration of the likelihood that gene doping will spread and of the means by which it might spread must also take account of potential obstacles, motives, routes of access, and gateways.

HEALTH RISKS AS AN OBSTACLE?

Common to all doping practice is the fact that the techniques and agents that underpin it were developed for the treatment of diseases and accordingly have not been studied in relation to use for performance enhancement in healthy individuals. Therefore, the health risks associated with misuse for doping purposes cannot be assessed on the basis of clinical drug trials. This is evidenced by the severe to catastrophic effects on health, in some cases leading to death, that have been seen in some athletes who have doped themselves.

From this point of view gene doping techniques could scarcely be riskier. At the same time, the principles that underlie the techniques used to bring about specific modifications of gene activity entail *specific risks* which, in the absence of empirical evidence, must be regarded merely as *scientifically plausible assumptions*. In this respect a distinction can be made between risks that arise as a result of insertion of genetic material into the organism (lack of tissue specificity on the part of vectors leading to uncontrolled spread of the foreign gene in the organism; mutations and immune reactions) and risks that result from overexpression (i.e. excessive production in the body) of performance-relevant biomolecules (e.g. promotion of uncontrolled cell growth). Given the complexity of the mechanisms that regulate gene activity, it is almost self-evident that manipulation of these mechanisms can result in a wide variety of side effects and thus potentially in severe damage to health.

Nevertheless, experience obtained with conventional doping practices casts great doubt on the notion that these imponderable health risks constitute an effective disincentive to the use even of scientifically unproven methods. Along with the prerequisite of availability, the crucial factors governing the use and spread of gene doping techniques are probably the presumed achievable effect – i.e. the potential improvement in performance – and (lack of) detectability (see below).

ROUTES OF ACCESS

Therapeutic techniques and drugs that are either already licensed or at least at the clinical trials stage would appear to be the most likely initial candidates for misuse for doping purposes. In order to predict which gene doping strategies could become relevant within what period of time, it would be important to monitor progress in research and development, especially in pharmaceutical companies, on a continuous basis. Nevertheless, it must be assumed that by no means all projects that could be relevant in terms of gene doping become known to the public (at least in their early stages).

Along with misuse of licensed therapeutic agents, another, and potentially even more worrying, possibility is emerging, namely a form of "individual" gene doping in which all the testing procedures that form part of the drug regulatory process are circumvented. An example of this would be a genetic-pharmaceutical manipulation designed specifically for a particular athlete or a small group of athletes – as in the Balco scandal, in which a small company produced "designer" steroids specifically for doping purposes and made them available to a small circle of elite athletes. Something similar could conceivably occur with gene doping, since at least in some cases the time and expenditure involved do not appear to be much greater than in the Balco case. Relatively simple methods include construction of virus-based gene vectors, production and administration of naked DNA, and construction of gene vaccines for the production of antibodies (e.g. to block receptors). These are all routine tasks for molecular biologists, and many of the individual steps can be performed using standard procedures and apparatus and commercially available kits.

A common objection to gene doping is that the methods used in it are not validated and in particular that enhanced performance has not been demonstrated either in normal subjects or in highly trained athletes. Nevertheless, results obtained in preventive research oriented towards doping practice show that even when the effectiveness of a particular doping strategy has been repeatedly denied (as in the case of growth hormone), athletes will continue to use it.

GATEWAYS: ELITE SPORT – BODYBUILDING – ANTI-AGING DRUGS?

Overall it can be assumed that gene therapy-like techniques (i.e. gene doping in the narrow sense) are very probably subject to considerably greater obstacles to abuse than are the many different techniques and pharmaceutical developments used for specific manipulation of gene activity. Given the present state of advancement of a number of projects being undertaken by the biotechnology and pharmaceutical industries, it must be assumed that such methods can already be misused for doping purposes, since – as is apparent from experience obtained with peptide hormones (EPO, growth hormone) – "abusers" can gain access to them in clinical studies.

In this respect it should be noted that abuse of myostatin inhibitors, for example, is far less likely to occur in competitive sport than it is in recreational sport, most notably in the world of bodybuilding, in the internet forums of which these new drugs have long been discussed and sought after.

In the longer term, a potentially far more important route of access than illegal appropriation of gene-modulating substances and techniques from clinical trials (or the sort of "individual" gene doping referred to above) could arise at the fringes of the treatment of age-related disabilities, e.g. the treatment of excessive muscle loss with (by then) licensed drugs. This area of medicine borders on and blends imperceptibly into what has become known as "enhancement", i.e. the nontherapeutic use of lifestyle drugs to improve everyday performance, which has become a socially and politically hot topic in recent times.

4. THE KEY QUESTION OF DETECTABILITY

When strategies for preventing and combating doping are being devised, a key question is whether, and if so how, gene doping can be detected. Past experience suggests that reactive development of detection methods is quite inadequate as a means of combating doping effectively. The WADA responded to this problem some years ago by establishing an international program to promote research into methods of detecting gene doping.

Techniques of gene therapy or gene modulation are aimed either at inserting a gene or a genetic element into certain somatic (body) cells and there activating it, or else at activating or inhibiting an existing gene or genetic element. Where the introduced genetic or gene-regulating element is chemically different from endogenous substances, direct detection should be both possible and qualitatively sufficient. However, due to the rapid pace of development in this field and the variety and complexity of gene modulation, most experts are of the opinion that techniques for direct detection are likely to become less important, since it would be far too expensive to test for all possible forms of genetic manipulation.

Most of the research projects currently being supported by the WADA are therefore aimed at developing indirect methods of detecting gene doping – though only one of the 20 such projects is aimed at detecting the vectors used, whereas all the others are aimed at detecting deviations from normal physiological conditions. Though theoretically plausible, approaches based on vector detection are subject to a number of problems. Firstly, attenuated human viruses, the most commonly used type of vector, are in some cases difficult to distinguish from naturally occurring viruses. Secondly, when employed in gene therapy viral vectors are used only in small amounts and where possible only locally in order not to precipitate an immune reaction. Detection of nonviral

vectors (naked DNA, siRNA) is likely to be far more difficult because of the short biological half-life of nucleic acids. At present it is entirely unclear whether or in what way detection might be possible in the case of gene doping techniques in which cells are removed from the body, genetically altered outside of the body, and finally returned to the body (*ex-vivo* techniques such as shown in Figure 2).

DETECTION OF NONPHYSIOLOGICAL CHANGES IN PARAMETERS

Whereas up to now certain easily measured parameters such as the concentration of red blood cells or of certain steroid hormones have been determined, in the future it will be necessary to obtain highly differentiated profiles of the levels of a huge range of molecules ("biomarkers") in blood and tissue samples taken from athletes in order to obtain information on the multiplicity of possible manipulations. Current research into possible means of detection is focused on the question of what characteristic changes in the body's molecular patterns occur after genetic manipulation. To this end the full repertoire of modern biomolecular analytical methods is used in order to obtain "molecular fingerprints". These are highly differentiated and specific analytical patterns of the DNA, RNA, or protein composition of samples of urine, blood, or tissue. The aim here is to describe the patterns that occur as a specific reaction to the administration of exogenous substances intended to alter gene activity and to distinguish such patterns from those that occur as physiological reactions to the administration of permitted substances and/or to permitted training methods.

This type of work, however, is still at a very early stage. So far, the development of usable tests has been defined as an objective in only one of the WADA projects (determination of total myostatin activity). Whether this whole approach will eventually prove successful cannot be predicted at present. As far as analytical tests are concerned, however, no alternative is presently in sight.

5. TESTING AND SANCTIONS

In many countries responsibility for combating doping in sport is divided between the world of sport and that of politics. The many anti-doping activities required in sport are harmonized and to a significant extent driven by the World Anti-Doping Agency (WADA). As long as five years ago the WADA took the precaution of including gene doping in its list of prohibited substances and methods (Prohibited List). Together with the World Anti-Doping Code (WADC), this list forms an important cornerstone of the repressive measures undertaken by organized sport and the state in their joint struggle against doping.

All the defined violations of the WADC anti-doping regulations are applicable to gene doping. Self-administration, refusal to undergo testing, possession, trafficking, admini-

stration to others, and participation in various other activities are prohibited. Sports organizations that have incorporated the WADC or the NADA code for Germany into their statutes or adopted similar agreements have thereby formally prohibited their members from engaging in gene doping. This is true of large sections of competitive sport, but not of individual sporting activity such as that practiced in fitness clubs and the like.

The Prohibited List has also been incorporated into German law. As a result of the November 2007 revision of the *Arzneimittelgesetz* (AMG, German Drug Law), the placing on the market, prescribing, or administering to others of substances included in the Prohibited List (including any attempt at such actions, as in the regulations governing trafficking, administering, and involvement in other activities) are likewise prohibited and subject to sanctions. The same applies to substances that are required for the use of the methods listed (including gene doping) (Section 6, Paragraph 2, AMG). However, there is no reference to Section 4, Paragraph 9, AMG, which defines and designates gene transfer agents as medicinal products.

In the particular case of gene doping the principal problem will lie not so much in prohibiting actions as in monitoring compliance with the prohibition and obtaining proof of violations that will stand up in a court of law (problem of implementation). The main tool available to sports organizations for monitoring compliance with these prohibitions is that of doping tests. The most reliable evidence that can be obtained by sports organizations is to be found in samples of body tissues and fluids on the basis of which a prohibited action can be demonstrated using detection methods that possess a sufficient degree of certainty. By contrast, the state enjoys broader investigative authority. Since doping tests and criminal prosecution violate the individual rights of the sportsperson, the nature of the prohibited action must be sufficiently precisely formulated (principle of clarity and definiteness). From the legal perspective it is doubtful whether the present definition of gene doping satisfies this requirement.

TABLE DOPING VIOLATIONS AND REGIMEN OF SANCTIONS IN GERMANY

Gene doping					
O… c… (bas…	…port …tion-internal …egulations …DC/NADA code)		Violations of anti-doping-regulations	State *Arzneimittelgesetz* (Section 6a)	
San…	Detection			Detection	Sanctions
Bans on …ing (two year… …ong, reduction… …in-ished res… …ity)	Doping tests (observation with the test)		Presence of a prohibited substance, its metabolites, or markers in the doping sample (Attempted) use of a prohibited substance or method Refusal or failure to have sample taken (Attempted) exertion of influence on doping test	Fundamental right to free development of one's personality and to freedom of association	
Warning to two years prohibition on competing			Violation of regulations on availability for out-of-competition testing		
Prohibition on competing (two years to lifelong)	Observation		Possession of a prohibited substance or method	Surveillance and prosecution	Up to three years of imprisonment or fines In serious cases one to ten years of imprisonment
Manager: withdrawal of accreditation, no official function: (at least four years to lifelong)		Gene doping	Trafficking of prohibited substance or method		
			…empted) administration of pro-…ited substances or methods or other action		

Gene doping: Nontherapeutic use of cells, genes, genetic elements, or of the modulation of gene expression having the capacity to improve athletic performance is forbidden.

Source: WADA/NADA code, *Arzneimittelgesetz*, Prohibited List (Federal Law Gazette 2007 Part II No. 18)

Detection of violations of anti-doping regulations is likely to prove far more costly in the case of gene doping than in that of present doping practices. The existing testing structures, which are based essentially on occasional urine tests, will probably not be sufficient. If gene doping is to be detected, the present system of in-competition and out-of-competition testing will need to be expanded. There will be an increased need for samples and the admissibility of obtaining samples (e.g. blood and tissue samples) will need to be assessed. In addition, the admissibility of newly developed specific diagnostic tests to detect gene doping will need to be assessed at the appropriate time. All in all, the entire process of detection of gene doping (demonstration both of the factual circumstances and of subjective guilt, e.g. of the athlete) is likely to make great demands on sports jurisdiction.

The state has the capacity to assist organized sport in the pursuit of cases of gene doping. The setting up and specific training of special police units and of specialized public prosecutor's offices for effective criminal prosecution of offenders, clearly defined contact routes and contact persons, and closer cooperation between prosecuting authorities and other relevant entities and individuals (science, sport, pharmaceutical manufacturers) are already important for combating conventional doping and will be absolutely indispensable in the fight against gene doping.

Since these repressive measures in the fight against gene doping will be very expensive and are still subject to a number of unresolved legal questions, they are by themselves unlikely to act as an effective deterrent against gene doping and will need to be supplemented by strategies to prevent gene doping from occurring in the first place.

6. NEED FOR INFORMATION AND ACTION

As a political issue, gene doping is characterized by incomplete and uncertain knowledge coupled with a pressing need for action. This situation is taken account of in the following examples of possible actions. If combined, these could form the building blocks of a specific strategy to combat gene doping.

- *Screening of biomedical and pharmaceutical development projects with particular reference to their potential relevance for gene doping*

  In gene doping, knowledge acquired via basic and/or applied research in the life sciences for the purpose of developing novel therapeutic strategies is misused. Continuous monitoring of biomedical and pharmaceutical development projects and of the potential demand for products that might lend themselves to gene doping could yield strategically important information. This could lead to a sort of "early warning system" that would provide points of reference for individuals involved in the fight against doping and for research on the prevention of doping. Willingness of industry to cooperate would be helpful in this regard.

- *Identify means of detection, develop tests, design intelligent monitoring systems*

  The detection of gene doping is a field in which a great deal more research and development is required. At present, a two-stage approach seems to hold the most promise. This consists of "intelligent" monitoring and – where there are grounds for suspicion – specific detection tests. Before such a monitoring system can be set up, clarification is required both of technical aspects (what parameters measured at what intervals provide evidence of doping-induced physiological changes or abnormalities) and of legal questions relating not only to sanctions but also to data protection and the safeguarding of individual rights. If this approach can be developed into a technically realizable monitoring system there is a prospect that the increasing number of doping – including gene doping – practices can be more effectively combated.

> *Develop concepts and activities for gene doping-specific public information campaigns (behavioral prevention)*

In parallel with the further development of testing and sanctioning structures, independent public information campaigns focused on gene doping need to be developed. If these are to have a preventive effect, a broad approach is required that takes account of the entire process of individual sporting development in which doping mentalities and modes of behavior can gradually arise. In such an approach attention must be paid both to the sportsperson's immediate milieu (trainer, manager, physician) and to the role of sponsors and the media.

> *Adapt support policies and tie these to specific conditions*

Sport as a whole, and elite sport in particular, receives support from a variety of sources. Public sponsors now require recipients of financial support to adhere to the anti-doping directives of the WADA and the NADA. Gene doping is thus covered to the extent specified in these directives. On the other hand, a demand for repayment in the event of a violation requires proof that will stand up in a court of law. Here again, the problem of detection is seen to be the Achilles heel of the matter. Despite this, decisions on how much public money to allocate and the conditions under which financial support is granted should be retained in all cases and if necessary should be made more restrictive in view of the possibility of gene doping. In this way the state's activities in supporting sport can serve as a model for sponsorship by the private sector.

> *Drug Law – check applicability and other statutory offenses*

The coming into effect of the *Gesetz zur Verbesserung der Bekämpfung des Dopings im Sport* ("law to improve the struggle against doping in sport") creates better conditions for the prosecution of doping, especially in the milieu of sportspeople. Nevertheless, gene doping as a prohibited activity needs to be more precisely defined in order to satisfy the principle of clarity and definiteness.

The broadening of the definition of doping to include substances that are intended for use by prohibited methods has resulted in the inclusion of substances used in such ways for the purpose of gene doping. In order to satisfy the principle of clarity and definiteness, reference could be made in Section 6a, Paragraphs 2 and 2a, AMG to Section 4, Paragraph 9a, AMG. In this way a prohibition of the use of gene transfer agents for the purpose of gene doping could be established.

In view of possible future developments, consideration should be given to the question of whether the factual characteristic "nicht geringe Menge" ("a non-small amount") should also apply to gene doping or whether instead any use of gene transfer agents in humans that is not medically indicated should be made a criminal offense.

In gene doping the broader topic of doping in sport is seen in more concentrated form. The German Bundestag and its committees are in a position to adopt a leading role in the political and social debate about gene doping. A proactive approach that is visible to the public could include taking the initiative in instigating additional research into the consequences and prevention of gene doping as a basis for possible political and legal measures.

The Office of Technology Assessment at the German Parliament (TAB) advises the Bundestag and its committees on matters relating to technical and social change. The TAB is an organizational unit of the Institute for Technology Assessment and Systems Analysis (ITAS) at the Karlsruhe Research Center, a member of the Helmholtz Association. The TAB has been working since 1990 on the basis of an agreement between the Karlsruhe Research Center and the German Bundestag and since 2003 has cooperated in subareas with the Fraunhofer Institute for Systems and Innovation Research (ISI), Karlsruhe.