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Nadezhda GORCHAKOVA
Dr. able of Medicine, Full Professor, Bogomolets National Medical University, Taras Shevchenko boulevard, 13, Kyiv, Ukraine, 01601 (gorchakova.na21@gmail.com)
***ORCID:** 0000-0002-7240-5862*

Igor BELENICHEV
Dr. able of Medicine, Full Professor, Head at the Department of Pharmacology and Medical Formulation with Course of Normal Physiology, Zaporizhzhia State Medical University, Stalevariv street, 31, Zaporizhzhia, Ukraine, 69035 (i.belenichev1914@gmail.com)
***ORCID:** 0000-0003-1273-5314*
***Scopus Author ID:** 6508296867*

Valeriia HNATIUK
Ph.D., Associate Professor of the Department of Pharmacology, O.O. Bogomolets National Medical University, prospect Peremogy, 34, Kyiv, Ukraine, 03057 (gvalery.nice@gmail.com)
***ORCID:** 0000-0002-5764-3600*
***Scopus Author ID:** 57193661449*

Sergij OLIYNYK
MD, PhD, Dr Sci, Full Professor, Research professor of Ewha Womans University Medical Center (EUMC), Seoul, Republic of Korea (sportmed1969@gmail.com)

Oleh KUCHKOVSKYI
PhD in Biology, Senior lecturer, Department of Pharmacology and Medical Formulation with the Course of Normal Physiology, Zaporizhzhia State Medical University, Stalevariv street, 31, Zaporizhzhia, Ukraine, 69035 (olegk181@gmail.com)
***ORCID:** 0000-0002-0548-0029*

Juliana MOSHKIVSKA
Teacher, Communal institution "Zaporizhzhia Medical Professional College" of Zaporizhzhia Regional Council, Zaporizhzhia, Ukraine

Eduard DOROSHENKO
D. Sci. in Physical Education and Sport, Head of Department of Physical Rehabilitation, Sports Medicine, Physical Education and Health, Zaporizhzhia State Medical University, Stalevariv street, 31, Zaporizhzhia, Ukraine, 69035 (doroe@ukr.net)
***ORCID:** 0000-0001-7642-531x*

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GENETIC DOPING: REALITIES, PERSPECTIVES OF APPLICATION IN SPORTS AND BIOETHICAL ASPECTS

The authors of the article, based on their own research, as well as taking into account the numerical results of other scientists, set out modern ideas about the use of gene doping in sports. In recent years, significant progress has been made in the use of gene therapy for the treatment of patients. However, some new substances can be used as gene doping in athletes. This provides greater physical endurance, the rapid growth of muscle mass, etc. It has been proven that such manipulations of genetic material and/or the introduction of recombinant proteins may be associated with health risks. In particular, great concern is caused by the potential impact of these substances on the human cardiovascular system, which can lead to catastrophic consequences, such as myocardial infarction. New developments by scientists have led to the appearance of tools, which directly affect the key links of success in sports – energy supply mechanisms and the quality and duration of effective muscle contraction. A potential benefit of genetic modification in sports is

the elimination or significant reduction of gender discrimination in sports. Although discrimination is likely to be an ongoing ethical problem, it is interesting that genetic manipulation may be a step toward finding a solution. The main argument in favor of genetic technology and its potential impact on gender discrimination in sports is that people whose genes are designed for athletic advantage can compete and be judged solely on athletic performance, thereby making gender a non-factor. Although research is currently limited and inconclusive, there is a tentative consensus that genetically modified athletes will have some advantage over non-genetically engineered athletes. In elite sports, this advantage, even if it is very small, can be decisive in close competition. Medical specialists from the WADA Anti-Doping Commission consider it their duty to warn athletes, coaches, and doctors about the serious danger associated with taking these substances. Don't let anyone be fooled by frivolous advertising and artificial hype surrounding these doping. They are deadly. Don't let anyone be fooled by frivolous advertising and artificial hype surrounding these doping. They are deadly. Don't let anyone be fooled by frivolous advertising and artificial hype surrounding these doping. They are deadly.

Aim. *The purpose of this study is to provide an up-to-date semantic analysis of our own results and literature data on the biomedical and bioethical aspects of genetic doping and the prospects for its use in sports.*

Key words: *sports pharmacology, genetic doping, types of gene modifications, pharmacological agents, pharmacological targets, bioethics.*

Надія ГОРЧАКОВА
доктор медичних наук, професор кафедри фармакології та клінічної фармакології, Національний медичний університет імені О.О. Богомольця, бульвар Тараса Шевченка, 13, м. Київ, Україна, 01601 (gorchakova.na21@gmail.com)
ORCID: *0000-0002-7240-5862*

Ігор БЄЛЕНІЧЕВ
доктор біологічних наук, професор, завідувач кафедри фармакології та медичної рецептури з курсом нормальної фізіології, Запорізький державний медичний університет, вул. Сталеварів, 31, м. Запоріжжя, Україна, 69035 (i.belenichev1914@gmail.com)
ORCID: *0000-0003-1273-5314*
SCOPUS ID: *6508296867*

Валерія ГНАТЮК
доктор медичних наук, доцент кафедри фармакології, Національний медичний університет імені О.О. Богомольця, просп. Перемоги, 34, 03057, м. Київ, Україна (gvalery.nice@gmail.com)
ORCID: *0000-0002-5764-3600*
SCOPUS ID: *57193661449*

Сергій ОЛІЙНИК
доктор медичних наук, професор, Медичний центр університету Ewha Womans, м. Сеул, Республіка Корея (sportmed1969@gmail.com)

Олег КУЧКОВСЬКИЙ
кандидат біологічних наук, старший викладач кафедри фармакології та медичної рецептури з курсом нормальної фізіології, Запорізький державний медичний університет, вул. Сталеварів, 31, м. Запоріжжя, Україна, 69035 (olegk181@gmail.com)
ORCID: *0000-0002-0548-0029*

Юліана МОШКІВСЬКА
викладач, Комунальний заклад «Запорізький медичний фаховий коледж» Запорізької обласної ради (moshkovska666@gmail.com)

Едуард ДОРОШЕНКО
доктор фізичного виховання та спорту, професор, завідувач кафедри фізичної реабілітації, спортивної медицини, фізичного виховання і здоров'я, Запорізький державний медичний університет, вул. Сталеварів, 31, м. Запоріжжя, Україна, 69035 (doroe@ukr.net)
ORCID: *0000-0001-7642-531X*

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ГЕНЕТИЧНИЙ ДОПІНГ: РЕАЛІЇ, ПЕРСПЕКТИВИ ЗАСТОСУВАННЯ У СПОРТІ ТА БІОЕТИЧНІ АСПЕКТИ

Автори статті на підставі власних досліджень, а також з огляду на численні результати інших науковців виклали сучасні уявлення про використання генетичного допінгу у спорті. Останніми роками було досягнуто значного прогресу у використанні генної терапії для лікування хворих. Однак деякі нові речовини можуть використовуватись як генний допінг у спортсменів. Це надає більшої фізичної витривалості, швидкого зростання м'язової маси тощо. Доведено, що подібні маніпуляції з генетичним матеріалом та/або введення рекомбінантних білків можуть бути пов'язані з ризиком для здоров'я. Зокрема, велике занепокоєння викликає потенційний вплив цих речовин на серцево-судинну систему людини, що може призвести до катастрофічних наслідків, таких як інфаркт міокарда. Нові розробки вчених призвели до появи засобів, які безпосередньо впливають на ключові ланки успіху у спорті – механізми енергозабезпечення та якість і тривалість ефективного м'язового скорочення. Потенційною перевагою генетичної модифікації у спорті є усунення чи значне зниження ґендерної дискримінації у спорті. Хоча дискримінація, найімовірніше, буде постійною етичною проблемою, цікаво, що генетичні маніпуляції можуть стати кроком до пошуку рішення. Головний аргумент на користь генетичних технологій та їхнього потенційного впливу на дискримінацію за ознакою статі у спорті полягає в тому, що люди, чиї гени створені для спортивної переваги, можуть змагатися та оцінюватись лише за спортивними результатами, тим самим роблячи ґендер не фактором. Хоча дослідження нині обмежені та непереконливі, є попередній консенсус щодо того, що генетично модифіковані спортсмени матимуть певну перевагу перед тими, хто не є продуктом генетичних технологій. В елітному спорті ця перевага, навіть якщо вона дуже маленька, може мати вирішальне значення в тісному змаганні. Фахівці-медики з Антидопінгової комісії ВАДА вважають за свій обов'язок попередити спортсменів, тренерів, лікарів про серйозну небезпеку, пов'язану з прийманням цих речовин. Нехай нікого не обманює легковажна реклама та штучний ажіотаж навколо цих допінгів. Вони смертельно небезпечні.

Мета дослідження полягає в тому, щоб зробити актуальний семантичний аналіз власних результатів та даних літератури з медико-біологічних та біоетичних аспектів генетичного допінгу та перспектив його використання у спорті.

Ключові слова: *спортивна фармакологія, генетичний допінг, типи генних модифікацій, фармакологічні агенти, фармакологічні мішені, біоетика.*

Relevance. Over the past few years, significant progress has been made in mapping the human genome. In this connection, more and more attempts are being made to use gene therapy in the treatment of patients (García-Nieto et al., 2019, p. 186). The goal of gene therapy is to replace defective genes *in vivo* and/or to stimulate the long-term endogenous synthesis of a deficient protein (Cantelmo et al., 2019, pp. 1093–1101). In vitro studies have shown that factors that enhance the expression of human recombinant proteins such as insulin (INS), growth hormone (GH), insulin-like growth factor-1 (IGF-1), and erythropoietin (EPO) may have therapeutic applications (Burke, 2019, pp. 156–165). Unfortunately, genetic methods developed for therapeutic purposes are increasingly being used in competitive sports (Brown, 2019, pp. 258–280). Some new substances (for example, anti-myostatin antibodies or nystatin blockers) can be used for gene doping in athletes. The use of these substances can cause an increase in body weight and muscle mass, as well as a significant improvement in muscle strength (Champer et al., 2020, pp. 24377–24383). Although it has been proven that uncontrolled manipulation of genetic material and/or the introduction of recombinant proteins may be associated with health risks, athletes are increasingly turning to prohibited gene doping (Lea & Niakan, 2019, pp. 1479–1489). At the same time, anti-doping research is being conducted in many laboratories around the world to try to develop and improve new methods of detecting gene doping in sports (Nieman, 2021, p. 2549).

Methods and methodology. Research methods – bibliosemantic, analytical, logical, and generalization methods. We explored the bibliographic database of life science and biomedical information MEDLINE, EMBASE, Medline (PubMed), the Web of Science, and Cochrane Central to search for English publications satisfying the keywords of this study. All authors independently selected articles, evaluated the quality of the data, presentation, and interpretation correspondence to the main idea of the study, and constructed the final list of references.

Scientific novelty. We for the first time carried out a semantic analysis of modern patent literature sources, as well as our own results, as a result of which promising pharmacological targets of various types of gene modification were identified. Materials on modern pharmacological agents are also summarized, the use of which contributes through the regulation of gene expression to increase the body's endurance.

Results of semantic analysis and its discussion. Thanks to the World Anti-Doping Agency (WADA) and other sports organizations, there is hope for real protection of athletes from the adverse health consequences of gene doping, which gives a chance to support the idea of fair play in sports (Kolliari-Turner et al., 2021, pp. 2221–2229). Two types of gene modification are discussed in the literature: somatic therapy and germline therapy. Modification of somatic genes is associated with the treatment or alteration of gene cells in adults. The modifications that occur as a result of this type of

gene therapy are limited to the individual and cannot be inherited by any future offspring (Kleiderman et al., 2019, pp. 508–513). An example of somatic gene therapy that violates WADA policy is modifying a cell to make it regularly produce more testosterone than it would naturally. The second type of gene modification is more controversial and is known as germline therapy (Read et al., 2020, p. 100175). The biggest reason for disagreement is that this type of modification is done before birth, and all manipulations with germline therapy become hereditary. The main function of germline modification is to counteract genetic disorders or hereditary diseases. For example, if there is a family history of heart disease, germline therapy can be used to change the genome of an unborn person. In this way, the risk of heart complications in later life can be reduced or even prevented. Somatic gene modification is a process that can only be used on existing humans. There have been reports that two substances have been discovered that can significantly increase muscle strength and endurance. One of these compounds has demonstrated the ability to improve physical performance in animals even in the absence of exercise. It was also possible to increase endurance in animals by introducing a modified version of the nuclear cell receptor PPAR-δ (PPAR-delta) gene into their genome, which regulates metabolic processes in cells (Lamas Bervejillo & Ferreira, 2019, pp. 39–57). Through a lengthy search, scientists only partially identified a chemical compound called GW 1516. Mice that received it did not show any extraordinary abilities without training, but after starting physical exercises, their strength and endurance increased much faster than in normal mice after the same loads. GW 1516 was discovered in the process of studying the mechanisms of the effect of new generation antidiabetic drugs on glycogen synthesis and glucose utilization (earlier the name GW 1516– GSK 516 – may well indicate the connection of the substance being studied with the action of the enzyme glycogen synthase kinase – GSK, which plays an important role in carbohydrate metabolism).

GW 1516 and AICAR rearrange the work of genes in the human body (Choi et al., 2019, pp. 633–638). Mice treated with these drugs ran 60–70% longer and farther than their normal counterparts. These substances affect the genes of muscle cells, and experiments on animals have shown that they supposedly significantly increase the body's endurance, many times surpassing in their effect all available "traditional" doping (Saha et al., 2021, pp. 195–204). Scientists are extremely concerned about the fact that the advertised magical properties of these drugs will lead to their rapid spread in the sports world. At the same time, there were not enough studies on the effects of drugs on the human body. In particular, great concern is caused by the potential impact of these substances on the human cardiovascular system, which can lead to catastrophic consequences, such as myocardial infarction. Medical specialists from the VFLA Anti-Doping Commission consider it their duty to warn athletes, coaches, and doctors about the serious danger associated with taking these substances. Don't let anyone be fooled by frivolous advertising and artificial hype surrounding these doping. They are deadly (Lin et al., 2021, pp. 2206–2222).

When AICAR and GW 1516 appeared in the scientific literature, the media called them "charge pills". In the most generalized form, the mechanism of their action is related to the influence on energy production processes. In particular, new substances increase the formation and subsequent oxidation of fats (lipids), which serve as one of the important sources of energy during physical exertion, and increase the speed of blood flow, which ensures the stable transport of lipids to the places of their metabolism. In addition, both AICAR and GW 1516 are associated with the processes of carbohydrate metabolism – the main energy substance during prolonged physical exertion (Belenichev, et al, 2022, pp. 145–157). It is known that muscle fibers are mainly divided into 2 types. "Slow", but type I endurance fibers require a good supply of oxygen and glucose and contain many mitochondria. "Fast" fibers of type II "get tired" quickly, but can work for a long time in anaerobic conditions, receiving energy due to the breakdown of glycogen (Plotkin et al, 2021, p. 127). There are fibers of both types in any muscle, but there are more "slow" fibers in the muscles of the trunk, which perform mainly static loads, and "fast" fibers adapted to dynamic loads in the limbs. The tendency to obesity and type 2 diabetes is associated with a decrease in the muscles of "slow" fibers, and scientists from two Californian and one Seoul university under the leadership of R. Evans, in search of a way to fight obesity, created a "marathon mouse" (Trommelen et al., 2019, pp. 185–197).

The biochemical mechanisms of the transformation of muscle fibers from one type to another under the influence of training were discovered quite recently (Adewumi et al., 2019, pp. 147–155). In particular, the signaling protein PGC-1-α, one of the transcription cofactors of the β-(or, as it is more often called, γ-) receptor coactivator of the peroxisome proliferation activator, plays a major role in this transformation (Kytikova et al., 2020, pp. 1–18). PGC is involved in the process of proliferation (growth and division) of mitochondria by activating another protein, PPARδ – the receptor for the peroxisome proliferation activator. The "delta variant"

was chosen because other isoforms of the same protein are much less effective in the process of converting muscle fibers: α- by 10 times, and γ by 50 times. To test how PPAR-δ will affect metabolism, scientists introduced its modified gene into mouse embryos, connected to the promoter (part of the gene that gives the command for its reading) of human actin – a protein that, together with myosin, ensures muscle contraction (Mirza et al, 2019, pp. 502–513). Without this, the gene could earn not in muscle, but in any other tissue. The protein synthesized in the muscles, which entered the adipose tissue in the bloodstream, effectively prevented its growth and accelerated fat burning: after 3 months of being on the "Atkins diet" (35% fat versus the usual 4%), transgenic mice gained three times less fat, than usual. In this, the structure of the muscle tissue has changed so much that it was visible to the naked eye from the biopsy. Due to the increase in the concentration of myoglobin, the transgenic muscles were noticeably redder than the same muscles of normal mice. The number of types I fibers in them was much more than usual (for example, in such a typically mixed fiber composition of the calf muscle, it was twice as much). The concentration of enzymes necessary for glucose oxidation and ATP synthesis also increased significantly (Neupane et al., 2019, pp. 1–10).

In conclusion, the author notes that "...as a result, without training, on the same genetics, lean and muscular transgenic mice could run 2/3 (per hour) longer and almost twice (per kilometer) farther than normal mice during treadmill training. And this is the result of the work of just one of the hundreds of genes that are being studied in the hope of developing treatments for hereditary diseases ... and that can be used to create genetically modified athletes".

All known types of gene doping, starting with the use of the recombinant erythropoietin gene, which accelerates the synthesis of erythrocytes and hemoglobin, and ending with the modification of vascular endothelial growth factor (VEGF) to accelerate the growth of new capillaries and arteries and, accordingly, indirectly (Fujii & Sato, 2020, pp. 156–169). New developments by scientists led to the appearance of tools that directly affect the key links of success in sports – energy supply mechanisms and the quality and duration of effective muscle contraction.

As of January 1, 2009, both of the above-mentioned substances were already included in item M 3 "Gene doping" of the WADA Prohibited List. And although earlier it was implied that when using gene doping, injectable forms are used, the two above-mentioned substances can be used in the form of tablets. What is GW 1516 and AICAR?

Analysis of scientific publications on the above-mentioned new types of gene doping (or, more precisely, chemical substances) showed that GW 1516, less often called GW-501516 or GSK-516 (in the Russian-language literature, sometimes GSK 1516), is an agonist of the activator of the proliferating peroxisome delta receptor (Peroxisome proliferator-activated) (Višnjić et al., 2021, p. 1095). Peroxisomes are cellular organelles that help the body get rid of toxic substances. Peroxisome proliferator-activating receptors are a family (PPARs) of compact protein molecules, which contain about 500 amino acid residues and are located near DNA inside cell nuclei (Moreno et al., 2021, p. 1030). Proliferators, that is peroxisome activators act specifically through PPAR. It is known that in molecular biology, the family of these receptors, which includes α-, β- (in the USA, the latter are called γ), and δ-forms of PPAR, is a group of nuclear receptors of proteins that function as transcription factors that regulate gene expression (a multistep process of conversion genetic information into a functional product, usually a protein) (Strosznajder et al., 2020, p. 86–98), in response to binding by appropriate activators – ligands (Fig. 1).

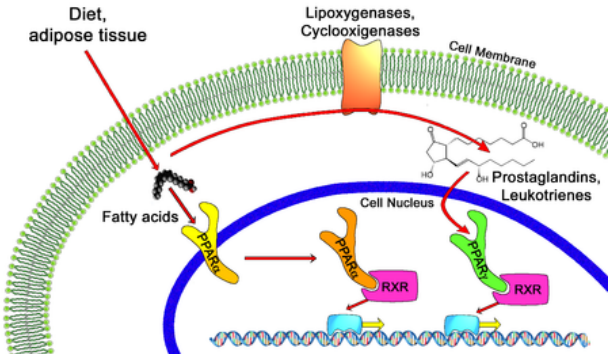

Fig. 1. The structure of the PPAR receptor and its binding to ligands

PPARs are activated by binding to ligands and then attaching to specific regions of DNA (Tripathi & Shrivastava, 2019, p. 420). When binding to a specific ligand, PPAR changes its conformation (structure), which allows one or more protein activators to be included. Each of the PPARs controls the activity of a certain ensemble of genes that control many processes of intracellular exchange, growth, and apoptosis (programmed cell death) of some cells, and several pathological processes, in particular, inflammation and carcinogenesis (Christofides et al., 2021, p. 154338). PPARs are important in the regulation of cell differentiation, transcription (reading of information embedded in genes), and metabolism of carbohydrates,

lipids, and proteins in higher organisms. All PPARs in molecular terms are closely related and associated with certain DNA structures (nucleotide sequences) of various genes, which enables PPARs to influence their transcription and expression (Cheng et al., 2019, p. 5055). The functions of PPARs can vary depending on the way their ligand is attached to the promoter part of the gene, as well as on the number of coactivators and corepressors (substances that contribute to inhibition of function) of proteins, the presence of which can stimulate the activity or hinder the functioning of the peroxisome receptor.

When it turned out that PPARs play a much more multifaceted role in the life of higher organisms, PPAR-activating agents were in turn called ligands (Korbecki et al., 2019, pp. 443–458). PPARα is mainly found in the liver, kidney, myocardium and skeletal muscles, and adipose tissue, and γ- and δ-forms of PPAR prevail in adipose tissue and skin, as well as in vascular endothelium (Choudhary et al., 2019, pp. 731–739). Since γ-receptors have three subtypes (γ1, γ2, and γ3, expressed in different tissues, it should be clarified that γ1 is present almost everywhere, but its action is especially noticeable in the heart, muscle tissue, small intestine, kidneys, pancreas, and spleen (Gao et al, 2020, p. 105328).PPAR-γ2 is maximally expressed mainly in brown adipose tissue, and γ3 – in macrophages, large intestine, and white adipose tissue, while searching for a molecular target for a group of agents called “peroxisomes” to increase tissue sensitivity to insulin regulation of fat metabolism (Wagner & Wagner, 2020, p. 1133).

PPARα and PPARγ are the molecular targets of many approved drugs, particularly those based on fibrates and thiazolidinediones, as noted. For PPARα, such agents are primarily fibrates (gemfibrozil, ufibrate, bezafibrate, etc.), widely used in the treatment of cardiovascular diseases, type 2 diabetes, obesity (Giampietro et al., 2019, pp. 1051–1066), and secondly, nonsteroidal anti-inflammatory drugs (NSAIDs), which are especially often used to relieve pain associated with damage to muscle and bone-joint structures. For PPARγ, which increases insulin sensitivity, synthetic activators are primarily thiazolidinediones, and to a lesser extent fibrate (Decara et al., 2020, p. 730).

In the living organism, one of the most important ligands for PPARs are free unsaturated fatty acids with a long chain: linoleic, linolenic, and arachidonic (mainly for the c-form) and eicosanoids (precursors and metabolites of prostaglandins and other similar biologically active ones). For example, PPARγ is activated by the prostaglandin PGJ2, and PPARα by the inflammatory mediator leukotriene B_4 (Hung et al., 2019, pp. 5497–5506).

PPARs play an important role in the metabolism of free fatty acids, triacylglycerols, and cholesterol in the body. Activation of the α-form of PPAR due to a change in the transcriptional activity of genes involved in lipoprotein metabolism contributes to a decrease in the content of atherogenic low-density lipoproteins (LDL) in blood serum, increases the activity of cholesterol transport from peripheral tissues to the liver (Carvalho et al., 2021, p. 805). The experiment showed that with PPAR deficiency under conditions of starvation, the concentration of glucose in the blood decreases by 50% after 24 hours, which indicates the important role of PPAR in glucose homeostasis. PPARα also has anti-inflammatory effects. These properties have been documented mainly in vitro experiments, as well as in animal experiments (Wang et al., 2020, p. 2061).

As for the action of substances that enhance the action of PPARs, it was recently demonstrated that in patients with type 2 diabetes mellitus, PPARα agonists of the fibrate structure reduce the risk of myocardial infarction and reduce the frequency of the need for coronary revascularization, which indicates the beneficial effects of these drugs in this categories patients. In model studies with isolated human cells in the background of stimulating overexpression of PPARα, it has not yet been determined whether activation of PPARα leads to adverse cardiac effects in humans, as noted in the animal experiment. At the moment, there is also no convincing scientific evidence that PPARα agonist therapy can increase the risk of developing chronic heart failure in humans.

It is known that drugs based on thiazolidinediones, namely pioglitazone and troglitazone (the latest generation – rosiglitazone, trade name Avandia) are among the most modern drugs for the treatment of type 2 diabetes. They increase the sensitivity of tissues to insulin, which allows you to control the level of glucose. Activation of PPARβwith the help of these drugs, regulates the transcription of insulin-sensitive genes, which are involved in the control of the synthesis, transport, and utilization of glucose. In addition, PPARβ ligands based on thiazolidinediones also affect the regulation of fatty acid metabolism. However, drugs of this class have some side effects, for example, hepatotoxicity, especially when the therapeutic dose is exceeded.

GW 1516, around which so many copies were broken in such a short period, i3s structurally 2-[2-methyl-1-4-([4-methyl-2-[4-(trifluoromethyl)phenyl)-1.3-thiazole-5)-yl] methyl sulfanyl-phenoxy-acetate with a molecular weight of 453.498 g/mol (Fig. 2).

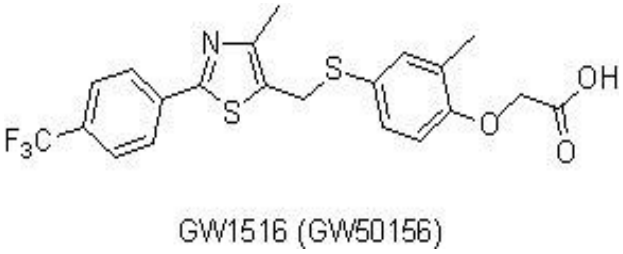

Fig. 2. Chemical structure of GW 1516

To date, the metabolism, bioavailability, half-life, excretion routes, teratogenic effects, and therapeutic doses of GW 1516 have not been described. This substance was developed jointly by employees of the Hugo and Salk Institutes in San Diego on behalf of the pharmaceutical corporation "GlaxoSmithKline" under the leadership of Professor Ronald Evans. Just one mention of a pharmaceutical company, which occupies one of the leading positions in the world in the production of many vital drugs, indicates that no one was specifically engaged in the development of doping substances, and the tasks of the research were purely therapeutic. The first reports about this substance appeared in the biochemical scientific literature in 2003. Research results published only in February 2008, demonstrated in obese men with prediabetes the possibility of reverse transformation of metabolic abnormalities by, most likely, stimulation of free fatty acid oxidation (Wondmkun, 2020, pp. 3611–3616). GW 1516 activates adenosine monophosphate-activated protein kinase (an enzyme involved in energy supply processes) and thus stimulates the absorption of glucose by skeletal muscle tissues, as well as the utilization of free fatty acids (Ishii et al., 2021, p. 0928). Phase II clinical trials are currently underway for the potential use of GW 1516 to prevent atherosclerosis and treat dyslipidemias. The results of the experiments showed the possibility of increasing the performance by 68% by using GW1516 when running mice on a treadmill.

Another prohibited type of gene doping is AICA ribonucleotide or AICAR (aminoimidazole carboxamide ribonucleotide) – an intermediate (intermediate product) of inosine monophosphate generation, which acts as an agonist of AMR-activated protein kinase (AM) (Moon et al., 2019, pp. 123–130). The substance AICAR stimulates the absorption of glucose in skeletal muscles and increases the expression of p38-mitogen-activated protein kinase types α and β, and also prevents the process of apoptosis by inhibiting the formation of free radicals, primarily chemically active atomic oxygen, inside the cell. It should be noted that a long time ago theoretical biochemists at the molecular level established a connection between the action of AMRK and the functioning of Na+-K+-ATP-ase (sodium-potassium pump), which hydrolyzes with the generation of energy 25% of all ATP reserves in the cell, and therefore AMRK activity is an ultrasensitive sensor of energy-dependent processes and reflects the processes of energy formation and, in particular, the lower limit of ATP formation, is inactivated by increasing the lower limit of the AMP/ATP ratio (Gunina et al., 2022, pp. 37–44).

According to the chemical structure, AICAR is a complex of compounds based on an imidazole ring with a ribonucleotide, namely 5-amino-imidazole-4-carboxamide-1-β-D-ribofuranoside (Fig. 3).

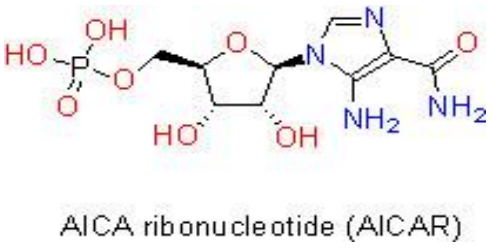

Fig. 3. Chemical structure of AICAR

In 2008, researchers at the Salk Institute under the leadership of Professor J. Kim found that AICAR, depending on the intensity of the load, when used for 4 weeks in experimental mice, significantly increases their performance on the treadmill in endurance exercises, apparently, the transformation of fast-twitch muscle fibers into more energy-efficient, lipid-generating, slow-twitch muscle fibers. It was shown that this process is mediated by the inhibition of palmitate-induced cell death (apoptosis) of endothelial cells by inhibition of lipid peroxidation in them (Su et al., 2019, pp. 1–13).

In an experiment on human and rat cells, it was established that AMRK regulates alveolar epithelial dysfunction stimulated by hypercapnia by CO_2 accumulation and, accordingly, improves pulmonary ventilation. Recent studies, in particular, conducted on isolated myocardial cells and muscle cells, show that AMRK also stimulates glucose uptake by these structures. It follows that effective agonists of AMP-activated protein kinase can be a point of application for the stimulation of energy supply mechanisms. As an activator of AMP-activated protein kinase, AICAR in an animal experiment increases the content of free fatty acids in both (fast and slow) types of muscle fibers due to a change in the levels of adiponectin and leptin (proteins involved in lipid metabolism) and an increase in the content of glucose in white muscle fibers (Fig. 4).

In addition, AICAR promotes an increase in the content of glucose, insulin, and free fatty acids, as well as a decrease

in lactate in the blood plasma of experimental animals (Fig. 5). The last fact can be very important for understanding the subtle mechanisms of energy supply for physical exertion and the mechanisms of restorative processes.

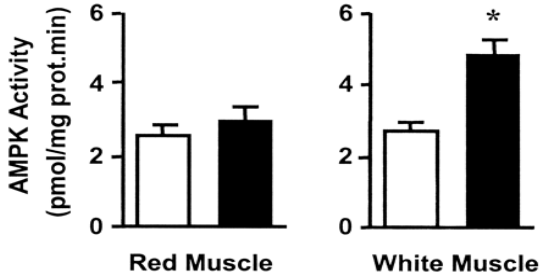

Fig. 4. Effect of AICAR on the activity of AMPK in white and red muscle fibers (the study was carried out in 2 groups – the main and control – with 6 animals in each. Changes are significant – *P< 0.01 compared to the control)

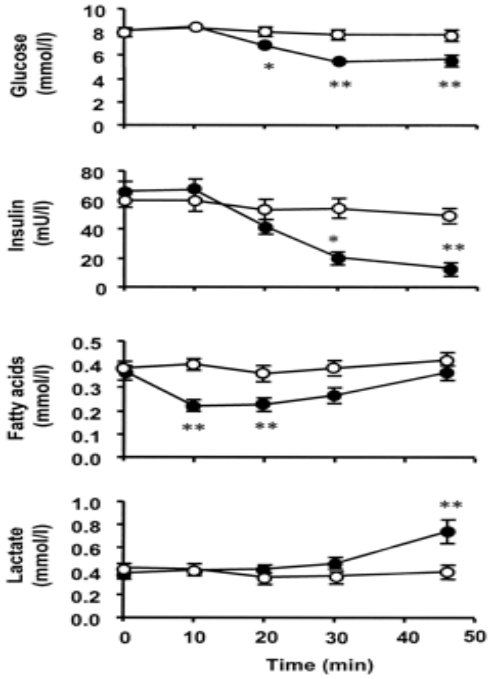

Fig. 5. The effect of AICAR on the plasma content of glucose, insulin, free fatty acids, and lactate (the study was carried out in two groups – the main and control – of 14 animals that were injected subcutaneously with AICAR. Changes are significant – *P < 0.05, **P <0.01 vs. control)

It should be noted that such research was conducted simultaneously in several scientific centers. So, back in 2005, it was shown that 5-amino-imidazole-4-carboxamide-1-β-D-ribofuranoside and phenformin activate AMP-activated protein kinase by inhibiting sodium transport in lung cells, which is one of the ways to maintain fluid balance in tissues (Yue & López, 2020, p. 2346). AICAR is also able to stimulate AMPK phosphorylation and activate glycolysis by increasing cellular glucose uptake. In conditions of low glucose content, an increase in the AMP/ATP ratio stimulates both processes in astrocytic brain cells. Activation (through a complex biochemical mechanism of TSC2 and mTOR modulator synthesis) of these signaling pathways helps conserve the amount of energy required for protein synthesis and glycolysis, thereby preventing neuronal cell apoptosis. The given data convincingly prove that the activation of AMRK with the help of agonists is accompanied by pronounced numerous effects on the part of various organs and systems, which can explain the multifaceted effect of modulators of the activity of this enzyme on the functional state of the body.

Practically simultaneously with studies of the physiological and biochemical activity of AICAR, the results of experiments also proved that in untrained mice AICAR, especially in combination with GW 1516, activates about 40% of genes that are activated during real intense physical exertion. The researchers concluded that when two agonists are used together, it may be possible to achieve a training effect without actual physical exertion (Schüttler et al., 2019, p. 1128). The results of these studies were published just before the Beijing Olympics (in August 2008) and indirectly indicated the possibility of using these substances as doping to stimulate the performance and endurance of athletes. In this regard, the leaders of the study urgently developed and handed over to the IOC and WADA tests for the detection of AICAR in the urine of athletes. Such actions of researchers cannot be explained only by the desire to create a substance prohibited in sports; rather, the side effect of substances being tested for the creation of new therapeutic drugs was revealed, which was expressed in triggering changes in the body, characteristic of physical exertion, and improving energy supply processes, especially due to lipids, as well as increased sensitivity to insulin. Currently, together with the Medical Commission of the IOC and WADA, it is developing a system of certification of tests capable of detecting the presence of metabolites of new gene doping agents – AICAR and GW 1516 (Huang et al., 2022, pp. 28767–28778).

The researchers believe that the benefits obtained with the use of AICAR and GW 1516 are due to the interaction between the cellular AMRK and PPAR-δ signaling pathways. Genetic analysis data support this hypothesis that AICAR and GW 1516 alone activate only a minor subset of genes expressed during exercise. At the same time, agonists of AMP-activated protein

kinase (AICAR) and the proliferating peroxisome- and, according to some data, PPAR (GW 1516) receptor (GW 1516) can imitate some of the indicative effects' characteristic of physical exertion. At the same time, the activation of both pathways (combination of AICAR and GW 1516 with exercise) leads to the expression of a significantly larger number of genes that remodel a large number of metabolic pathways in the body, including the metabolism of muscle tissue (Domoto et al., 2020, p. 1388).

Back in 1997, the IOC and sports doctors discussed the concept of "doping", and also tried to formulate where the boundary between the formal and real limits of reasonableness and validity of the use of those ergogenic means, which are listed in the WADA Prohibited List, is constantly expanding, passes. So, the story of the emergence of new types of doping, now genetic, is far from new (Simon & Dettweiler, 2019, pp. 497–500).

However, until there is convincing evidence in clinical trials, what negative effects can be caused by the use of AICAR and GW 1516, what can be reasonable doses and side effects of drugs based on these substances, as well as whether the resulting genetic modifications can be fixed and reproduced, it is not possible, probably unequivocally reject the possibility of using drugs based on AICAR and GW 1516 in sports, especially higher achievements. On the contrary, in the book of V. Templeton "Gene & Cell Therapy" (publishing house "Marcel Dekker", 2003, 1140 p.) the most important role of genetic modifications and the use of substances that modify the body's response is convincingly proven in the treatment of many serious diseases, including type 2 diabetes, atherosclerosis, hemophilia, Alzheimer's and Parkinson's diseases. The latest scientific works on this topic provide data that do not yet prove the presence of negative effects of AICAR and GW 1516 on the cardiovascular and other body systems; on the contrary, the authors believe that drugs based on this can become the "gold standard" for the treatment of diseases of the heart and blood vessels (Sahin et al., 2019, pp. 1047–1056).

Conclusion. Thus, it can be concluded that perhaps the use of genetic activity stimulators opens a new era in the development of the physical capabilities of athletes and increases the spectacle of sports competitions, especially taking into account the fact that the limit of the human body's own capabilities has already been practically reached.

The idea of creating and engineering the embryos of future athletes seems like a topic for science fiction or television. Surprisingly, the technology for this is currently being developed. However, the use of this technology would not make much sense if the benefits did not outweigh the risks of such a procedure. However, parents may be willing to take some risks when it comes to modifying their germline to increase their child's chances of becoming a star athlete and eventually finding themselves in a stable financial position. Parents who adhere to this point of view should take into account a very important caveat: genetics as such do not necessarily lead to athletic success. Other factors, such as ambition, diet, willpower, practice, and training, are also necessary to achieve success in sports. In American culture, it is normal to dream more and wish for the better. In this cultural mindset, the creation of "super-athletes" is not far-fetched and is a real reason for people wanting to use genetic technology in sports.

A very practical and probably more obvious reason for using genetic technology in sports is to help with recovery and injury prevention. Miah suggested that gene therapy could be used to help athletes recover more efficiently and effectively from injury. Early experimental studies, although limited, provided some supporting evidence, and Cieszczyk et al. agreed that gene therapy would help in the treatment of sports-related injuries such as knocks or concussions. The implementation of gene therapy in this way for sports is more in line with the original goal of scientific research to prevent and treat diseases.

A potential benefit of genetic modification in sports is the elimination or significant reduction of gender discrimination in sports. Although discrimination is likely to be an ongoing ethical problem, it is interesting that genetic manipulation may be a step toward finding a solution. The main argument in favor of genetic technology and its potential impact on sex discrimination in sports is that people whose genes are designed for athletic advantage can compete and be judged solely on athletic performance, thereby making gender a non-factor. Thus, gender will no longer be a determining factor in sports as genetic engineering levels the playing field (Wang et al., 2020, p. 2061).

With the development of so-called gene doping and cyber technology continuing, we may be facing a future in which sport (as we know it) exists in its purest form; that is, when athletes are judged only by their athletic performance and not by their gender, and where it becomes impossible to distinguish athletes based on their physique and gender identity (López et al., 2020, pp. 801–811). If genetic modification is allowed as a method of performance enhancement,

the elite sport will certainly look new with new challenges (Ma et al., 2020, p. 107502). Although research is currently limited and inconclusive, there is a tentative consensus that genetically engineered athletes will have some advantage over non-genetically engineered athletes. In elite sports, this advantage, even if it is very small, can be decisive in a close contest. Since the physical qualities of genetically enhanced athletes will not be as necessary for development, it will be necessary to pay additional attention to psychological training with an emphasis on motivation and concentration (Doudna, 2020, pp. 229–236). Elite sports and competitions could potentially become more exciting and showcase more highly developed athletes as a result of this new technology if allowed. Decision-makers in the field of sports management are faced with a very difficult task. There are certain risks and benefits associated with genetic modification, and those who study ethics in sports have no shortage of opinions on the subject.

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Moshkivska J. – writing a chapter on the bioethics of genetic doping and the WADA anti-doping program;
Doroshenko E. – writing essays on genetic modification in sports, the negative impact on the athlete's body.

Електронна адреса для листування з авторами: gorchakovan1941@gmail.com