

Genomic Technologies in Improving the Efficiency of Animal Health and Husbandry

(Article Review)

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Abstract - One of the reasons for this lag in the practical application of the accumulated technologies seems to be the lack of a concept of successive stages of their application in order to increase efficiency and reduce the time for traditional selection work. The first stage of such a technological chain should be a set of methods that allows selecting and selecting animals with an increased likelihood of the desired manifestation of the characteristics of productivity and adaptive potential in their offspring. In order to forecast productivity at the present time, particularly in dairy cattle breeding, "genomic selection" methods are used when, based on the genomic scanning by mononucleotide substitutions (SNP), groups of polylocus genotypes are combined, combining bulls with high milk productivity of their daughters. Genetic engineering is the name of a group of techniques used to identify, replicate, modify and transfer the genetic material of cells, tissues or complete organisms.

Important applications of genetic engineering in animal breeding are: 1) Marker-assisted selection (MAS). The objective of this technology is to increase disease resistance, productivity and product quality in economically important animals by adding information of DNA markers to phenotypes and genealogies for selection decisions. 2) Transgenesis, the direct transfer of specific genes/alleles between individuals, species, or even Kingdoms, in order to change their phenotypic expression in the recipients. Compared to the 'traditional' improvement techniques based on phenotypic information only, these *gene-by-gene* techniques allow theoretically a more complete management of animal genomes for animal breeding. In spite of high expectations and new technical developments, its actual efficiency is not always high, as they require a thorough knowledge of functional genomics, and pose additional technical, economical and ethical problems. The possible role for cloning adult animals in breeding is also discussed.

Keywords - Biomarkers, Quantitative Trait Genes (QTL), Health, Genomic Selection, Landscape Genomics.

I. INTRODUCTION

The material considers modern directions of application of molecular genetic methods in working with agricultural animal species. The directions of application of genomics methods for revealing genes associated with adaptive characteristics of animals are discussed, as well as with the

desired manifestation of signs of productivity. There is a need for close cooperation between molecular biological, clinical and selection studies to increase their effectiveness.

At the moment, biotechnology is gaining an increasingly important role in increasing the profitability of livestock. The introduction of the results of biotechnological research

into livestock production takes place primarily in the following areas of activity:

1. Improve animal health through biotechnology;
2. New advances in the treatment of humans using biotechnological animal studies;
3. Improving the quality of livestock products through biotechnology;
4. Advances in biotechnology in the protection of the environment and conservation of biological diversity.

Animal biotechnology involves working with a variety of animals (livestock, poultry, fish, insects, pets and laboratory animals) and research techniques - genomics, genetic engineering and cloning.

The development of molecular biology, in particular molecular genetics, has led to changes in many concepts about the ways and methods of predicting and treating diseases in both humans and animals. Medical molecular biology, as well as veterinary medicine, in the past few decades has reached an accelerated pace of development. There are qualitatively new methods for diagnosing genetically determined diseases, the spread of infectious agents, as well as the prevention and treatment of various diseases.

Changes in the search for new methods of treatment, in general, boil down to several main areas. These include increasing the accuracy, "targeting" of therapeutic agents at different levels of biological material organization, ranging from short regulatory nucleotide sequences, methods of "targeted" transgenesis, fitting a synthetic drug to the protein domain - key mediators of the cascade of pathological changes, biopreparations in order to force out pathogens from the metagenome of multicellular organisms. In its essence, this direction is the development of the work of Paul Erlich (1854-1915), who dreamed of finding a "golden bullet" for infectious agents, as well as altered cells in the development of cancer processes.

Another close to this, but less "repressive" trend is the development of therapeutic means for correcting pathological changes in the metabolom (a set of metabolic reactions) based on the accumulation of information on the key links of pathological biochemical changes, such as defects in antioxidant systems, reduced activity of detoxification enzymes and others. This direction is associated with the development of new methods of helping multicellular organisms by activating their own defense systems, which are directed not so much at the targeted

destruction of the "aggressors" (pathogens, own modified cells), but on the alignment of such a line of therapy that allows its own cellular populations, including and symbionts, to block the pathogenic process. Interestingly, the founder of this trend was, as is known, Ilya Ilyich Mechnikov (1845-1916), who created the theory of cellular immunity, rehabilitation with the help of the "Bulgarian rod", who developed the theory of autotrophic nutrition of man and other works [2]. It is natural that Paul Ehrlich and I. Mechnikov together became Nobel laureates in 1908 "For works on immunity" in the field of physiology and medicine.

II. THE CREATION OF GENETICALLY MODIFIED ANIMAL PRODUCTS REGULATED

In the United States, the health of farm animals is monitored by three government bodies: The US Department of Agriculture (USDA) monitors veterinary medicine, the development and production of vaccines and diagnostic tests; The US Food and Drug Administration (FDA) reviews and approves new medicines and nutritional supplements; The Environmental Protection Agency (EPA) provides control over pesticides and other means for the destruction of fleas and other parasites. Orders of regulatory bodies for animal biotechnology are reviewed by the Office of Science and Technology Policy Development with a view to harmonizing the activities of government bodies to ensure a rational scientific approach. Despite the huge amount of products being developed, there are not so many regulatory documents in printed form. In 2003, the FDA Center for Veterinary Medicine published a preliminary version of the guidelines for risk assessment in the cloning of cattle and the safety of eating foods made from meat from cloned animals. Specialists of the FDA came to the conclusion about the suitability of meat and milk for cloned animals to eat. The next step is to fully resolve risk assessment issues and proposals for the risk management process.

III. GENOMIC FOR IMPROVING ANIMAL HEALTH

To date, according to experts, the market for biotechnological veterinary products is 2.8 billion US dollars. It is expected that in 2005 this figure will increase to 5.1 billion. As of July 2003, 111 biotechnological veterinary products were registered on the pharmacological market, including killed bacterial and viral vaccines. Every year, the veterinary industry invests more than \$ 400 million in research and development of new drugs.

IV. FARM ANIMALS: CATTLE AND POULTRY

Biotechnology provides fundamentally new approaches to improving animal health and productivity of livestock and poultry. This improvement is possible due to the improvement of diagnosis, treatment and prevention of diseases; use of high-quality feeds from transgenic varieties of fodder plants; as well as by increasing the efficiency of breeding new breeds.

The modern veterinary industry has a huge set of tools for the prevention and treatment of diseases that are potentially capable of causing epizootic and death of agricultural livestock. Timely diagnosis and treatment in combination with proactive preventive measures helps reduce the costs of food production, as well as improve the health of animals in general and, accordingly, improve food safety. Biotechnology allows farmers to immediately diagnose the following infectious diseases by means of tests based on DNA typing and determining the presence of antibodies: brucellosis, pseudorabies, diarrhea, foot-and-mouth disease, bird leukemia, bovine rabies and trichinosis; soon veterinarians will have at their disposal biotechnological means for the treatment of various diseases, including foot and mouth disease, swine fever and mad cow disease; new biological vaccines are used to protect animals from a wide range of diseases, including foot and mouth disease, diarrhea, brucellosis, pulmonary infections of pigs (pleuropneumonia, pneumonic pasteurellosis, enzootic pneumonia), hemorrhagic septicemia, avian cholera, pseudocholera, pest and infectious diseases in artificial conditions of fish; active work is being done to create a vaccine against the African disease of livestock, dubbed the East Coast fever. If successful, this vaccine will be the first drug to combat protozoa and, at the same time, the first step towards the development of an antimalarial vaccine; molecular methods for the identification of pathogens, such as genomic fingerprinting, can monitor the spread of the disease within the herd and from the population to the population and identify the source of the infection; Genetic analysis of the pathogenesis of animal diseases leads to an improved understanding of the factors that cause diseases not only animals, but also humans, and approaches to control them; improved sorts of forage plants with the help of biotechnology provide an increase in feed nutrition due to the additional content of amino acids and hormones in them, leading to an acceleration in the growth of animals and an increase in their productivity. Biotechnological methods can improve the assimilation of coarse fodder. Scientists are working on new plant varieties to create edible vaccines for farm

animals. In the near future, farmers will be able to feed pigs with genetically modified alfalfa, which stimulates specific immunity to a dangerous intestinal infection. Researchers are working on a vaccine that could serve as an alternative to castration of cattle. Calves are castrated in order to reduce aggression, and pigs - to avoid the appearance of a specific odor that makes inedible meat of uncastrated boars. The new vaccine will ensure sterilization of animals without surgical intervention, without at the same time adversely affecting the growth of animals. In addition to diagnostic tests, vaccines and medicines used to maintain the health of farm animals, biotechnology plays an increasingly important role in breeding new breeds.

Methods of genetic mapping allow identifying genetically resistant to various diseases of animals and using them in breeding projects to obtain a healthy disease-resistant offspring. On the other hand, animals with genetic defects can also be identified and removed from the selection process. New DNA tests allow detecting pigs suffering from genetically determined pig stress syndrome characterized by trembling and death of animals under the influence of stress factors; inherently unfavorable signs of livestock can be identified using DNA tests currently used in national breeding programs in Japan. With their help, it is possible to detect a defect in the adhesion of leukocytes, characterized by recurrent bacterial infections, growth retardation and death during the first year of life; deficiency of coagulation factor XIII; hereditary forms of anemia and growth retardation of cattle.

V. INCREASING THE PRODUCTIVITY OF LIVESTOCK

Heads of livestock farms are directly interested in increasing the productivity of farm animals. Their ultimate goal is to increase the number of products (milk, eggs, meat, and wool) without increasing the cost of maintaining the livestock. The increase in muscle mass with a simultaneous decrease in the amount of fat in the body of meat animals since time immemorial is the goal of breeders. Biotechnology helps to improve the productivity of livestock through a variety of breeding options. For the beginning, individuals with the desired characteristics are selected, after which, instead of traditional crossing, sperm and eggs are collected and subsequent in vitro fertilization. A few days later, the developing embryo is implanted into the uterus of a surrogate mother of the appropriate species, but not necessarily of the same breed. Sometimes the embryo is divided into several parts, each of which is implanted separately. This form of cloning has been used

for several decades to quickly improve the genetic characteristics of farm animals.

Genomics methods are also used to improve traditional breeding approaches. In 2003, the first nucleotide (SNP - single nucleotide polymorphisms) polymorphism, first tested with a meat-cattle gene, was officially registered. The SNP method is used to identify gene clusters responsible for the formation of a particular trait, for example, for frying an animal. After that, using methods of traditional breeding, breeds are derived, in this case, characterized by increased muscularity. Throughout the world, active work is under way to sequencing the genomes of various animals and insects. In October 2004, the successful completion of the Bovine Genome Sequencing Project was announced. In December 2004, sequencing was also successfully completed use of genomic information in animal improvement. The use of genomic information (sequences or DNA marker polymorphisms) for the genetic improvement and selection of animals requires the knowledge of the effect of physically mapped genes with effects on economically important traits or quantitative trait loci (QTL).

This information is also required in order to effectively use transgenesis and MAS for genetic improvement (Lynch and Walsh, 1998; Montaldo and Meza-Herrera, 1998; Van Marle-Koster and Nel, 2003). In MAS, the genomic information is combined with the classical performance records and genealogical information to increase selection accuracy, performing selection earlier in life and reducing costs (Boichard et al. 1998; Elsen, 2003). The traits on which the application of marker-assisted selection can be more effective, are those that are expressed late in the life of the animal, have low heritability, are sex-limited, are expensive to measure or are controlled by a few genes. Examples are longevity, carcass traits in meat producing animals, and diseases or defects of simple inheritance. Expected increments in selection response from MAS for a single complex trait, using known QTL genotypes plus linear model predictions (BLUP), compared to selection on BLUP alone, ranges from -0.7 to 64 percent. In practice, results will depend on many parameters which are likely to be very different for each trait combination and population (Montaldo and Meza-Herrera, 1998; Dekkers and Hospital, 2002).

The statistical properties of genetic evaluations (predictions) of animals for quantitative traits obtained through mixed model methodology using phenotypic records and genealogical information as inputs are known as

BLUP. Best -means minimum variance of prediction, Linear -because predictions are linear functions of observations, Unbiased -means that the expected value of predictors obtained with linear model have an expected value equal to the expected value of the mean of the breeding values, conditional to data, and Prediction -because involves prediction of random breeding values). Most experiments on QTL detection in animals allow only the estimation of wide chromosomal regions (practical maximum resolution is of about 1 cM, but usual resolution is about 30 cM) that harbour a QTL in a 'statistical sense', estimated from the effects of some marker haplotypes on quantitative traits (de Koning et al. 2003). Thus, further confirmation is required in order to assure the use of the causative gene. Identification of the causative gene has proven to be difficult. The process to identify the gene responsible for the effect is known either as 'fine mapping' studies (targeting mapping smaller genomic regions) or 'candidate gene' studies (targeting individual genes based on their probable function) (Lynch and Walsh, 1998). In practice, MAS is useful to select genes with effects well identified and precisely located in the genome such as those controlling monogenic recessive diseases such as the pig stress syndrome gene. However, for most recessive alleles with lethal or semi-lethal effects, natural selection will maintain their frequencies very low (Hartl and Clark, 1997) making MAS unnecessary. Unless the additive and non-additive effects for most genes involved in the phenotypic expression of complex, economically important traits are determined, MAS should be regarded just as a tool to increase the rates of genetic gains and not a method to fully open the 'black box' of the genetic control of complex traits, that would render phenotypic selection 'obsolete'.

Therefore, the perspectives on the optimum use of DNA marker information in the framework of a genetic program is still a matter of debate. Quantitative trait loci experiments using crosses between breeds or lines with extreme genotypes for a trait, increases the power of detecting QTLs for that trait, compared to within-family designs. These across population's polymorphisms are not necessarily useful to perform MAS for within-population selection. The favourable allele could be fixed in parental populations and crosses may be commercially irrelevant. Wide genome scans for positioning a QTL using crosses or within-family experiments, are only the initial phase of the search for a true mayor gene involved in a complex trait (de Koning et al. 2003). Another source of complexity for detection and use of QTL for selection is genetic heterogeneity, where DNA mutations in several sites produce the same

phenotype. Major single gene effects can be sometimes compensated in the organism using alternative metabolic pathways (McAfee, 2003).

In recent years, in connection with the need to intensify livestock, global ecological changes, the spread of monobreedity and genetic erosion of breeds, the relevance in livestock development of the application of all these areas has increased significantly. Despite the fact that their origins date back to the end of the 19th and beginning of the 20th centuries, research trends and their applied significance have not changed, but the creation of new tools and methods has made it possible to move to a new scale of research into the field of nanobiotechnology [1]. In connection with the methods of sequencing genomes, the direction is actively developing, the essence of which is related to the hopes to allocate such biomarkers whose control could allow predicting the resistance of organisms not only to infectious diseases, but also to other, abiotic, unfavorable environmental factors. The modern stage of the transition from genetics to genomics, from working with individual genetic elements to a comparative analysis of whole genomes, opens new possibilities in studying genetic structures, their dynamics in different groups of living organisms and solving traditional problems of veterinary and selection. Earlier, a limited number of molecular genetic markers of polymorphism, as a rule, encoding sequences of structural genes (groups) were used most widely to identify biomarkers for resistance to various diseases, to create genetically grounded programs for preserving gene pools of breeds of agricultural animal species, to eliminate errors in origin, to control and speed up the selection process blood, electrophoretic variants of proteins), in the future, - anonymous DNA markers, then, genotyped e microsatellites.

The Applied Biosystems Company (www.appliedbiosystems.com), in consultation with the Food and Agricultural Organization (FAO) and the International Society of Animal Genetics (ISAG) for cattle, has developed a test system for genotyping 11 microsatellites (purchase of appropriate equipment, programs analysis and consumables). The advantage of these microsatellites is obvious, since their localization on cattle chromosomes is known (microsatellites: TGLA227, BM2113, TGLA53, ETH10, SPS115, TGLA126, TGLA122, INRA23, ETH3, ETH225, BM1824). Usually such work included genotyping, on average, about 10 loci. One of the main sections of breeding farm animals is the study of the breed as a whole and interconnected group of animals. The interrelationships between the abundance of

rocks and the rate of genetic improvement, the evolution of wide-zone large and small local breeds, and the structure of the rock are studied, especially in connection with the introduction of large-scale selection methods. The most important contribution to the practice of animal husbandry is the development of methods for breeding new highly productive breeds of farm animals. With the introduction of large-scale breeding and the increasing opportunities for rapid reproduction of animals with a valuable genotype, the principles of breeding new breeds, developed by Ivanov, have become even more important. The breeding of new highly productive animal lines that meet certain conditions promotes the improvement of the species. The doctrine of the constitution of animals develops.

Methods are developed for predicting the future productivity of animals in the early stages of ontogeny, which make it possible to improve the efficiency of selection. The promising direction of breeding of farm animals is the development of methods for increasing the resistance of animals to diseases. The mathematical methods, modern computers, which allow modeling the processes of selection-breeding work and the system of managing the breeding business as a whole in breeds, are increasingly used in the cultivation of farm animals. The nature of the interaction of the animal genotype and the environment is studied, which makes it possible to evaluate the quality of animals under different conditions, to determine the reliability of the genotype evaluation when the habitat of descendants changes, etc. Studies of the origin and domestication of agricultural animals, which has not only a historical biological but also a practical importance as a prospect of domestication of some wild animals (bison, bison, elk, fur-bearing animals, etc.). The work on remote hybridization of animals is closely connected with this problem. The development of immunogenetics, cellular engineering. Transplantation of early embryos, fertilization of the egg and early development of embryos "in vitro" make it possible to separate blastomeres to produce genetically ideal individuals; methods of manipulating the nucleus of the cell (nuclear transplantation, removal of one of the pronuclei, etc.) - to change the heredity of animals in a directed manner. Prospective studies on the stimulation of parthenogenesis for the production of gomizygotic animals. This direction of farming animals will allow genetic copying of farm animals. Work is underway to apply genetic engineering methods to livestock breeding.

In recent years, methods of simultaneous genotyping of several animal DNA polymorphisms, flanked by inverted Inter-Simple Sequence Repeat (ISSR-PCR) or terminal

regions of mobile genetic elements (IRAP-PCR), have been widely used in the DNA matrix of a single animal polymorphism. Thanks to the development of methods for using DNA-microarrays, on which millions of reference DNA fragments are attached, tens of thousands of mononucleotide polymorphisms (SNP) are now successfully evaluated in one genome. The totality of these methods was called "genomic scanning" and provided an opportunity to switch to comparing genotypes not by piece genes or loci, but, simultaneously, by whole genomes. In recent years, genomic scans have become a major trend in modern evolutionary and population genomics. Genomic scanning can vary from the use of several tens or hundreds of markers to true genomic scanning by full sequencing of genomes. The most successful method of genomic scanning is Affymetrix, which developed and launched a biochip for the detection of trace amounts of meat from 12 species of mammals, 5 species of poultry and 16 species of fish. Among the developments of this company there is a biochip, which allows detecting mononucleotide polymorphism (SNP) on 20 thousand sites in different parts of genomes of dairy and meat breeds of cattle. Bovigen, for example, has been successfully working in this direction, for example, it has created biochips to identify genes associated with the quality characteristics of cattle meat, as well as biochips to control the origin of animals.

To date, about 30,000 bulls of the Holstein breed have been genotyped using the BumineSNP50 BeadChip DNA microarray from Illumina, which allows the simultaneous genotyping of 54,001 SNPs (~ one SNP per 50,000 base pairs). These DNA microarrays (chips) detect not only SNP-linked markers, but also variability in the number of copies of the corresponding genomic regions where SNPs are localized (copy number variations - CNV, include deletions, duplications, translocations and inversions). CNV in humans covers 12% of the genome (data are presented in the Database of Genomic Variants (<http://projects.tcag.ca/variation/>)), that is, the variability of CNVs involves more nucleotides per genome than SNPs.

Spontaneous CNV occur on average with a frequency of 1/10,000 base pairs [13, 16]. Given the higher frequency of occurrence of CNV, it was hoped that this new generation of polymorphism markers of various regions of genomic DNA would allow increasing the resolution of the mapping process of the main genes of such characteristics of agricultural animal species as resistance to biotic and abiotic environmental factors, thus, significantly affect the success of breeding work. Genomic scanning of genomes of agricultural animals. species is widely used in recent years

to address the following main tasks: determining the parameters of variability within and between breeds; identification of the geographical location of individual populations and / or mixing populations with different genetic origins; obtaining information on evolutionary relationships (phylogenetic trees) and finding out origin centers and migration routes; the mapping of genes, including the identification of carriers of known alleles of genetically determined diseases, as well as of alleles and genes associated with increased resistance to infectious and non-infectious diseases; establishing the origin and genetic relationships (eg DNA fingerprint) within the population; support genetic improvement in animal populations using markers; creation of DNA-storages for the purposes of research and storage of genetic resources.

Full sequencing of the cattle genome, carried out in 2009 as a result of the work of the international consortium Bovine HapMap, led to a promising discovery for the search for biomarkers of increased resistance and productivity of animals. It turned out that the genome of cattle differs markedly from the genomes of six other mammalian species by enrichment with segmented duplications. And, for a number of genes associated with the immune system, an increased number of copies is found in cattle. These include the beta-defensin genes, interferons and lysozyme genes involved not only in antibacterial protection (nonspecific immunity), but also in the destruction of cellulose in the four-chamber stomach [14, 15]. Due to the development of genome scanning methods a new term appeared - "genomic selection", which attracted special attention in the field of breeding specialized dairy breeds of cattle. Currently, it involves the use of DNA matrices (DNA-biochips) to genotyping about 50,000 mononucleotide substitutions (SNPs) in the detection of genomic regions, the SNP genotypes associated with the desired manifestation of the characteristics of milk production.

In fact, this trend is a continuation of work on mapping the main genes of milk productivity, started in 1990 with the use of genotyping first dozen, then hundreds of microsatellite loci, which continue to this day, despite the receipt of quite contradictory data. Now such searches are developing using the methods of genomic scanning, DNA of microarrays (biochips). It should be noted that one DNA microarray for scanning the genome of one animal on average for different companies of their manufacturers costs about 200 euros (excluding other consumables, depreciation of appropriate instrumentation and the costs of skilled labor for their use).

The effectiveness of searching for biomarkers of dairy productivity is still quite debatable, primarily due to the physiological and genetic complexity of its characteristics. To date, a map of genes involved in the formation of the mammary gland and milk on the chromosomes of cattle (lactem) has been created. The analysis included 197 genes of milk proteins and more than 6,000 genes involved in the development and function of the breast [8].

The subdivision of all these genes into 238 segments of chromosomes in which QTL-Quantities Trait Loci were localized made it possible to reduce the search space for genes whose polymorphism is associated with the variability of milk production characteristics by more than an order of magnitude. It turned out that the genes involved in milk productivity and the QTL complex of milk productivity characteristics, revealed in various studies, actually cover all 30 chromosomes of cattle. The comparisons of the genomes of the platypus, opossum, placental mammals (cattle, dog, man, mouse, rat) performed in the same work made it possible to reveal gene losses and duplications, phylogenetic connections, sequence conservatism and their genes by the genes of milk proteins and involved in the formation of the mammary gland evolution. Data have been obtained that, in the genome of cattle, the genes of milk and breast proteins are evolving more slowly compared to other types of placental species studied. It was found that in these species, as well as segmental duplications, the genes of milk proteins, which determine the nutritional and immunological properties of milk, were the most divergent, associated with the processes of milk secretion.

Difficulties in using genomic selection are also due to the fact that dairy production itself depends to a great extent on environmental factors. Thus, Belgian researchers have shown that estimates of the breeding value of bulls in the milk productivity of daughters of the Holstein breed differ significantly in Luxembourg and Tunisia, with the share of the genetic component of variability in milk productivity higher in Luxembourg, and paratypic in Tunisia. Rank correlations in the same bulls were low and unreliable between the estimates obtained for them on the milk productivity of their daughters in different countries [4-6]. At the same time, data continues to accumulate, indicating a sufficiently low information content of the principle of mapping the main genes of quantitative traits, including, and using tens of thousands of SNP markers (for example, [17]).

Apparently, for the work with agricultural animal species, the most promising are the enormous possibilities of gene and genomic methods that allow identifying genes

and their combinations involved in adaptation that participate in the formation of population-genetic characteristics of numerous biological systems. In 2003, three articles emerged, essential for the integration of ecology, evolution and population genetics (genomics). Lukart and co-authors [9] defined the field of population genomics as "simultaneous study of multiple sites or regions of the genome in order to better understand the role of evolutionary processes that affect changes in genomes and populations." Feder and Michell-Olds [3] designated the synthetic discipline Ecological and Evolutionary Functional Genomics (EEFG). The main task of EEFG is to use all genetic and genomic tools to identify the subtle functional genetic changes involved in the evolution of adaptations. Landscape genomics was born from an alloy of methods of population genetics and covering geographic information systems geographic information systems (GIS) [10]. Landscape genomics has focused primarily on clarifying how different landscapes affect the gene flow of neutral genetic variants, usually with the goal of identifying populations that are threatened with extinction in order to preserve them.

In recent years, a number of data have been accumulated using the methods of landscape genomics, which allowed obtaining new information on the ways of settling agricultural animal species, allowing investigating the relationship between the features of the genetic structures of rocks and intra-group groups and the features of the ecological and geographical regions of their settlement. For example, a comparative analysis of the geographical distribution of allelic variants of 26 mononucleotide polymorphisms (Single Nucleotide Polymorphisms - SNP), localized in structural genes in 16 goat breeds of Italy, Albania and Greece. Ultimately, 12896 genotypes in 496 individuals were genotyped and analyzed [12]. Statistical analysis revealed a significant correlation between genetic distances based on the distribution of allelic variants and geographical distances between the groups of animals of different breeds studied. In addition, the cluster analysis showed that the rocks are grouped according to their genetic structure according to geographic origin, with the exception of the Greek "skopelos". The authors come to the conclusion that the history of geographic movements of animals played a major role in the formation of the modern genetic structure of rocks. Westward animal flows along the coastal route to Italy through Greece may have led to the formation of a gene flow of the studied goat breeds along the Northern Mediterranean.

In times of rapid global and unforeseen environmental change, the development of a viable policy for the conservation of the genetic resources of agricultural animal species, based on a global analysis of them, is necessary. Most local breeds are adapted to the characteristics of the habitat and the local conditions of the production system, but they quickly disappear. At the same time, they represent an important gene pool resource for solving emerging new breeding tasks and problems of adaptation to new ecological conditions. In this connection, based on the estimates of polymorphism and genotypes of 105 microsatellite loci, a comparative analysis of the genetic structures of 16 cattle breeds covering the geographical region from the Mediterranean domestication center was made, from Anatolia, through the Balkan and Alpine regions, to the North-West of Europe [11].

The analysis includes factory, commercial breeds that are under the influence of intensive artificial selection and local breeds reproduced according to traditional breeding patterns. It was found that the greatest genetic diversity is observed in ancient local breeds associated with the Podolian offspring of gray steppe cattle in the Anatolian regions and rocks of the Balkan regions, in comparison with the Alpine and Northwestern European breeds. In traditional breeds, the greatest number of rare allelic variants is preserved, reflecting initially their greater effective number. The obtained data testify to the special importance of preserving local, genetically heterogeneous rocks close to the initial centers of domestication of animals, from the standpoint of the need to develop a global and long-term strategy for the conservation of animal genetic resources, not only for cattle, but also for other agricultural species. It is known that in future decades the conditions for food production, especially for dairy farming, will change significantly in the event of predicted climatic changes, in particular, a rise in temperature.

This is especially true for dairy farming in Australia. It has long been known in this region that the breeding value of animals, estimated, including by the productivity of offspring, in dairy cattle breeding can vary significantly depending on the temperature regime of their content. In order to search for possible genetic mechanisms of adaptation of dairy animals to elevated temperatures in Australia, genomic studies have been performed in different regions of Australia, differing in meteorological data [7]. With climate warming, it is expected that due to water shortage, energy costs for obtaining dairy products will also increase. In order to search for molecular genetic markers associated with high temperature resistance of the general

characteristics of milk production, an analysis of the results of genomic scanning using genotype estimates for several thousand sites of mononucleotide polymorphism (SNP) with data on the resistance of dairy production to different environmental conditions was performed. Data on dairy production, meteorology and multiple genotypes from parents and daughters, who gave milk in a wide range of production conditions in Australia, were combined [7].

The ranges of dairy production in Australia range from completely pasture systems, to those based solely on fattening grounds, and from tropical to temperate climates. The work used three groups of data: records of daily milk yield for the first lactation of 62,343 Holstein-Friesian cows-descendants of 798 bulls, the same records of a daily milk yield of 35,293 Jersey cows, daughters of 364 Jersey bulls and a database of the Australian geo-information project (Queensland Office of the Ministry of Protection Environment and Resources - Queensland Department of Environment and Resource Management DataDrill, which combines maps of temperature and humidity across Australia. These data made it possible to calculate the index of temperature and humidity during the days of milking the cows and assess the effect on productivity and consumption of high-temperature food for them. In previous works of the same authors it was shown that from the change in the frequency of respiration, stress effects are found in dairy animals when the temperature / humidity index exceeds 60 units. Further, the authors compared the sensitivity of daughters of specific bulls to changes in milk yield and feed intake, depending on the temperature / humidity index. At the next stage, 798 Holstein-Friesian bulls and 364 Jersey bulls were genotyped using DNA matrices (Illumina BovineSNP50 beadchip), including 56,000 SNP.

The final sample included in the analysis included genomes of 781 and 362 bulls of both breeds, respectively, genotyped at 39,048 SNP. An analysis was made of the associations between genetically linked SNPs and the sensitivity of dairy daughters to changes in the humidity / temperature index and identified areas flanked by SNP whose polymorphism was statistically significantly associated with such variability. The most pronounced such a connection was found in both studied breeds in regions of chromosomes 9 and 29. Further, using the data of GenBank, the localization of structural genes in these areas was elucidated. One of these markers, most closely associated with the sensitivity of milk production to the moisture / temperature index, was localized on chromosome 29 in the area of the fibroblast 4 growth factor (FGF 4).

This gene is involved in the regulation of the control of apoptosis of the cells of the epithelium of the mammary gland in the processes of its development and involution after the cessation of lactation. Interestingly, a human expression of the same gene is described, besides the mammary epithelium, also in the epithelium of the testicles, in which its transcription substantially increases with increasing temperature and it is assumed that this gene performs a protective role for the sex cells, protecting them from the damaging effects of hyperthermia. The most distinctly associated candidate gene with variability in animal sensitivity to different moisture / temperature indices is found on chromosome 9 in the localization region of the glycerol-3-phosphate dehydrogenase-1 (G3PD-1) gene, which is involved in carbohydrate and lipid metabolism and is a key energy supply gene cells.

It is known that in mice with normal activity of this enzyme a long carbohydrate diet leads to hyperglycemia, hyperinsulinemia and islet hyperplasia in the pancreas, in contrast to mice mutant in this gene, which does not have such manifestations, but increases the sensitivity to insulin. Given the fact that insulin sensitivity differs significantly in cows that differ in the dairy response to the feeding level, the authors of this study [7] suggest that SNP mutations in this candidate gene (G3PD-1) or in areas associated with regulation of its expression, can lead to a change in insulin sensitivity and, in turn, to changes in milk production in response to the level of feed intake in cows. Thus, as a result of the performed studies using genomic scanning and GIS technologies, the authors succeeded in revealing two genes - a candidate for controlling variability in milk production in response to changes in humidity / temperature in animals of two specialized dairy breeds of cattle. The obtained data testify to fundamentally new opportunities for identifying genes and metabolic links associated with the adaptation of animals to unfavorable environmental conditions.

At the same time, insufficient knowledge of the structural and functional organization of genomes, network relationships between different genetic elements within genomes and environmental factors often leads to a reassessment of the ability to identify universal biomarkers for identification, therapy and prognosis for the development of a number of diseases, as well as the success of genomic selection in agriculture. To increase the effectiveness of such developments, the interaction between researchers of various fundamental biological processes, both on the scale of biomolecules, and clinicians and breeders of a broad profile, becomes critical. Main problems

related to the use of molecular genetics in the improvement of agricultural populations (Dekkers and Hospital, 2002; Dekkers, 2004; Pollak, 2005) are: Direct use of a discovered QTL effect for selection across families is not possible. By the time the information about the inferred genotypes is known, frequently the animals involved in the study are not available as candidates for selection, because they will be too old. Advantage from within-family selection for a QTL bracketed by markers over BLUP or phenotypic selection alone is frequently low and the methodology to exploit this information for selection is complex and relatively inefficient. There are statistical estimation errors, causing both false positive and false negative effects, particularly when the effect of the QTL is small. There is a lack of consistency of the effect of the same QTL between studies, caused by QTL by genetic background (epistasis) of QTL by environment interactions. The net economic effect of the QTL may be lower than the effect on single traits, because unfavourable effects on other traits. Selection using QTL is more complex than phenotypic selection alone.

QTL information (whether the information on the QTL is direct or indirect), adds to the list of traits used as selection criteria. Issues such as reduction of selection intensities and relative emphasis given to each trait, make optimal selection more difficult, with a need for adequate relative weights for the QTL, and the polygenic portions of the genetic variation for each trait at each generation (year). Short-term gains due to MAS may be at the expense of medium to long-term polygenic responses for important traits. Even with an unambiguous knowledge for the allele effects of a mayor gene on a complex trait, expected advantages from optimum use of genotyping alleles for a QTL for a multi-generation selection horizon is not always high. The polymorphism for the α s1-casein in goats has a strong effect on protein content and total protein output. The difference between homozygous for the highest and lowest effects for milk protein is approximately three phenotypic standard deviations for milk protein content (Barbieri et al. 1995; Manfredi et al. 1995).

Favourable alleles have frequencies lower to 0.5 in populations undergoing selection, making a very favourable case for potential gains in protein content and production from MAS using this polymorphism. Simulation studies by Larzul et al. (1997), Fournet et al. (1997) and by Manfredi et al. (1998) indicated that when an efficient 'conventional' progeny testing selection program is underway for increased protein production, the advantages from MAS are low to moderate. Maximum possible increase on total genetic gain for protein yield was 26%. Dekkers and Hospital (2002)

emphasized the overlap that exists between marker and phenotypic information for the improvement of a multi-trait goal over several generations, using MAS. A very optimistic prospect from use of MAS as well as other biotechnologies is very common in popular commercial and non-refereed publications, based on approaches based on exploiting single gene effects, without consideration to polygenic effects, economic values or time for fixation. Research shows that the real situations are far more difficult for complex traits. These traits are controlled by several genes and environmental effects (Montaldo and Meza-Herrera, 1998).

Dekkers (2004) made a survey on the status of application of MAS in actual animal breeding programs for complex traits. He concluded that initial expectations for the use of MAS were high, but the current attitude is one of cautious optimism, with a need for careful examination of alternative selection strategies, business goals and integration of molecular and other technologies. Pollak (2005) made a detailed survey on the application of DNA technology for beef cattle improvement in USA. He concluded that current contribution of the new DNA technologies for beef cattle breeding is marginal, because they are encountering logistics and mechanical issues. For genomics technologies to impact fully on the beef industry, a higher level of sophistication of the genetic tests will be needed. Tests based on the genes themselves, rather than DNA markers associated with genes, will be required (Moore and Hansen, 2003). It is theoretically possible to predict accurately the breeding values of animals using many markers (Meuwissen et al. 2001). From this knowledge, it is possible to develop a model for in vitro genetic improvement of animals. This is known as velogenetics. The model involves in vitro selection of cells containing the desired genes the use of totipotent embryonic stem cells (ES). The procedure uses transfection of the desired genes, selection in vitro of the cells, and nuclear transfer of the desired genotypes into receptor oocytes. This approach is supposed to increase the rate of genetic improvement by obtaining many generations in a short time by avoiding rearing, reproduction and selection of 'real animals' (Kingham, 1998; Smidt and Niemann, 1999; Visscher et al. 2000). Selection on the basis of genomic information only, such in this in vitro system, even with major genes with known effects well localized, may be dangerous, because in these artificial populations, unlike in real populations, natural selection would not be allowed to act at each generation on fitness traits under real, perhaps changing, environmental conditions. Changes on

economically important traits will not be evaluated directly (Dekkers and Hospital, 2002).

This may potentially reduce the responses on selected traits because of genotype x environment interactions (Montaldo, 2001). This is because selection is performed in artificial conditions that may deteriorate the fitness of the population and economic response. Using MAS for improving health in animals by reducing disease prevalence (increasing disease resistance) or increasing resilience (the ability to withstand the disease without harmful effects), for infectious or parasitic diseases has been difficult. In most cases, excepting some rare examples such as Scrapie in sheep, complete resistance could not be obtained with the manipulation of a small number of genes. For most diseases, single-gene approaches are expected to have only a partial contribution. Gene interactions are common (Kuhnlein et al. 2003). For many diseases, heritabilities are often low. That indicates the existence of many environmental factors affecting both the probability of infection and the response of the host. In spite of responses attained using conventional selection for some traits that are used as indicators of disease, the result is not well known. The existence of contradictory results regarding associations between production and disease resistance, the complexities of immune and resistance mechanisms and the interaction with other methods of control such as vaccination, sanitation, management and chemotherapy, makes the whole issue of selecting for disease resistance more difficult, in principle, that selecting for production traits. Moreover, we know that heritable resistance or resilience to more virulent form of pathogens would be increased by natural selection. As heritabilities for survival are generally low, we know that the genetic control of disease may be very complex, making difficult to change the outcome by manipulating single genes. There is one published result on a successful MAS selection program to reduce the prevalence of dermatophilosis, a tropical infectious disease in Zebu cattle (Maillard et al. 2003).

Maillard et al. (2003) argue to have obtained a sharp reduction in clinical prevalence of the disease from 0.76 to 0.02 in a period of five years by selecting against only two types II BoLA alleles associated with a high susceptibility of the disease. The authors explained the observed change resulting from selection performed in an unknown number of animals of each sex in 1996. However, a complete description of the changes in allele frequencies and genotypes from the moment of selection and their association with the evolution of prevalence by sex is not given. Considering the possibility of environmental changes

and the presence of natural selection, in the absence of a control group, it is difficult to know if the observed change is the sole result of the mechanisms invoked by the authors through MAS. We cannot at this moment forecast precisely the future of MAS in animal selection, but it is premature to conclude that methods based on phenotypic information will be replaced by methods based solely on genomic data (Smith et al. 2003; Van Marle-Koster and Nel, 2003).

An integration of both types of data with the use of more sophisticated statistical models is needed. It is far from sure that total replacement of phenotypic information with gene-by-gene information, as selection criterion is possible or even desirable in the future. Other very important applications of genetic markers in animal improvement include the optimization of mating strategies for non-additive genetic effects (estimation and managing of inbreeding and heterosis), parentage determination, genetic characterization of diverse animal breeds and populations using studies of between and within population (breeds) diversity (Oldenbroek, 1999) and marker-assisted introgression of particular alleles (Andersson, 2001; Dekkers and Hospital, 2002). Use of genetic engineering for animal and plant improvement is in its infancy, therefore many questions regarding efficiency, safety and societal benefits in particular situations remain. Problems arising transgenic plants, including their lower-than expected productivity, are reviewed thoroughly by McAfee (2003).

Simplistic and overoptimistic views of biotechnology should be replaced by serious and scientifically based assessments of these new technologies by potential users on a case-by-case basis. We need to emphasize that in most cases, the use of MAS is not a revolution but just an evolution with regard to the traditional methods, because we are looking to improve more efficiently traits that already are actually or potentially improved in an efficient way using, for instance, mixed model (BLUP) based technologies for selection. Efficiency issues are very important. In order to increasing the efficiency of MAS, we need previously to: Define with greater precision the selection goal and selection criteria (Monin, 2003). Optimize the use of BLUP and other 'classical' breeding methodology. The use of transgenic animals' models for the study of gene regulation and expression has become commonplace in the biological sciences. Contrary to the early prospects related to commercial exploitation in agriculture, there are some challenges regarding their use that still lay ahead (Archibald and Haley, 2003; Sang, 2003; Sillence, 2004). The risks at hand can be defined not only by scientific evidence but also in relation to public concern (whether perceived or real) that

exists in some people (Larrère, 2003). Therefore, the central questions will revolve around the proper safeguards to employ and the development of a coherent and unified regulation of the technology.

VI. CONCLUDING REMARKS

The development of molecular biology and genetics, elucidation of the structure and function of nucleic acids and proteins led to a qualitatively new application of biological organisms in production. Scientists have come close to solving the most important problem of heredity management based on genetic engineering. It is time that biologists, like the designers of new technology, can create living organisms with pre-planned properties. Methods of cell, chromosomal and genetic engineering have been developed that allow organisms to be modified by affecting whole cells, their nuclei, chromosomes, chromosome regions, genes and parts of genes. There was an opportunity to implement in a new way, in a new way, the tasks of agriculture, medicine and the microbiological industry. Based on modern discoveries in biochemistry, molecular biology, genetics, microbiology, it makes a significant contribution to the development of agricultural production, microbiological industry, medicine, environmental protection, the use of biological sources for energy production.

The main directions of biotechnology are microbiological synthesis, cultivation and use of plant and animal cells, genetic engineering, applied enzymology (the science of protein substances of cells). Depending on such a change, the action of the protein in the chain of biochemical reactions is strengthened or weakened, which in turn changes the manifestation of the sign of productivity in one direction or another. Long-term studies have established that in farm animals there are several hundred thousand such markers, an average of one per 50,000 nucleotides, which are evenly distributed throughout the genome. To quickly obtain information about the genomic profiles of the animal, Illumina and Affymetrix have developed DNA chips that allow the typing of the animal genotype for more than 50,000 SNP markers. In recent years, a new branch of genetics genomics has been born, which studies not individual genes, but whole genomes. The achievements of molecular biology and genetic engineering gave a person the opportunity to read genetic texts in the beginning of viruses, bacteria, yeast fungi, multicellular animals. For example, knowledge of the genomic structure of pathogenic bacteria is very important in the creation of rationally designed vaccines, for diagnosis and other medical purposes.

Most of the important potential technical advances offered by genetic engineering technology in animal breeding are still ahead. Their use has both advantages and problems. Advantages are related to a more complete control over the animal genome. Problems are related to technical complexity, high costs, in some cases, public acceptance and ethical dilemmas. It is not likely that this technology, will replace 'conventional' methods for genetic improvement. Instead, they probably will begin to be gradually incorporated into current genetic improvement programs that use efficiently classical improvement methods to achieve particular objectives.

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