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ASSISTED REPRODUCTIVE TECHNOLOGIES: THE HISTORY AND ROLE IN THE DEVELOPMENT OF GENETIC TECHNOLOGIES IN CATTLE

(review)

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The development of "active" transgenesis technologies has allowed targeted modifications (gene editing, GE) in the genome of farm animals belonging to different species with relatively high efficiency (reviewed by S.Y. Yum et al., 2018; A.L. Van Eenennaam, 2019; N.A. Zinovieva et al., 2019). However, effective improvement of livestock production systems based on GE technologies requires the development of an integrated approach that combines biotechnology, population genetics, quantitative genomics, and assisted reproductive technologies (ARTs) (C. Rexroad et al., 2019). The development of ART, including germ plasma collection for gene editing in animals, the effective production of GE-offspring, and their possible earlier multiplication are an integral requirement for the successful development and implementation of GE technologies in cattle breeding (A.L. Van Eenennaam, 2019). This review provides a retrospective analysis of the development of ART, including artificial insemination (R.H. Foote, 2002; R.G. Saacke, 2012; P. Lonergan, 2018), embryo transfer (K.J. Betteridge, 2003; R. J. Mapletoft, 2013), *in vitro* production of embryos (IVP) (L. Ferrй et al., 2019), oocyte retrieval in living animals (Ovum-Pick-Up) (R. Boni, 2012; M. Qi et al., 2013), and somatic cell nuclear transfer (C.L. Keefer, 2015; K.R. Bondioli, 2018; A.V. Lopukhov et al., 2019). We describe the state of the research and discuss the areas requiring further improvement in ART for the development of genetic technologies in cattle breeding, including gene editing. This review shows that for more than 100 years, significant progress has been made in the development of ART for cattle, many of which are now actively used in practical animal breeding (C. Smith, 1988; L. Ferrй et al., 2019) and became the basis for the development of effective programs for genetic improvement of livestock, including genomic selection (P.M. VanRaden et al., 2009). Current research priorities are focused on ensuring further progress in cattle breeding through the integration of GE technologies into livestock breeding programs (C. Rexroad et al., 2019, A.L. Van Eenennaam, 2019). ARTs are expected to play a crucial role in this ambitious task.

Keywords: cattle, assisted reproductive technologies, gene editing

Advancements in genetic technologies, including genome editing (GE), for application in agriculture and, in particular, animal breeding is one of the important goals of science and technologies around the world [1, 2]. Genomic

selection has become one of the most significant scientific advances in the last decade and has been implemented in practical animal breeding [1, 3]. One of the most promising scientific breakthroughs that can be achieved in the next decade is associated with the "ability perform routine gene editing of agriculturally important organisms" [4, cited according 1]. The development of "active" transgenesis technologies, such as CRISPR (clustered regularly interspaced short palindromic repeats)/Cas9 (CRISPR-associated protein 9), has allowed the incorporation of targeted modifications (gene editing, GE) in the genome of farm animals of different species with relatively high efficiency [reviewed by 5-7]. However, effective improvement of livestock production systems based on GE technologies requires the development of integrated approaches involving biotechnology, population genetics, quantitative genomics, and advanced reproductive technologies [1]. The development of assisted reproductive technologies (ARTs), including collection of germ plasma for GE from animals with the desired genetic characteristics (for example, having a high breeding value due to economically important traits) and the effective production of GE-offspring and their possible earlier multiplication are an integral requirement for the successful development and implementation of GE technologies in cattle breeding [6].

This review provides a retrospective analysis of the development of ART, describes the state of the art research, and discusses the areas for further improvement in ART to enable the development of genetic technologies in cattle breeding, including GE.

In its early stages, the main goal of ART was to increase male fertility. The first such technology, which was applied in livestock species, was artificial insemination (AI). Several reviews have described in detail the history of AI in cattle [8-10]. In the present paper, we briefly focus on the milestones involved in the development of this technology.

The development of AI in mammals began in 1780, when the Italian physiologist (professor of natural history) Lazzaro Spallanzani (1729-1799) performed AI in a female dog for the first time, resulting in offspring [11, cited according 12]. In 1799, John Hunter (1728-1793) successfully employed this method in humans, which resulted in the birth of a healthy child [13, cited according 12]. The first application of AI which can be received from one male in mammals to increase the number of offspring dates back to the late 19th century. In 1885, the breeder of Basset hounds sir Everett Millais (1856-1897) divided a single ejaculate into three parts and inseminated three female dogs, all of which successfully gave birth to offspring [14, cited according 12]. At about the same time, a French veterinarian demonstrated the effectiveness of AI for improving fertility in horses as well [15, cited according 16]. Further development in AI technology was achieved thanks to the works of a reproductive biologist from Cambridge, Walter Heape (1855-1929), who performed experiments on dogs, rabbits, and horses [12]. The practical bases of the AI for domestic animals were laid in 1899 by the Russian scientist Ilya Ivanovich Ivanov, who proposed the application of this method for multiplying the offspring from the best males to accelerate the improvement of breed qualities and productivity of animals [17, 18]. The ideas of I.I. Ivanov were further developed by V.K. Milovanov, who implemented large-scale AI projects in cattle and designed the first artificial vagina, similar to what is used nowadays [19]. By 1938, approximately 1.2 million cows were artificially inseminated in the USSR annually.

The role of AI in improving the genetic characteristics of domestic

animals was further increased by the proof that animal spermatozoa remain viable after freezing (cryoconservation) and storage at low temperatures. In 1942, the ability of the spermatozoa of higher vertebrates to maintain fertilizing capacity after freezing and thawing was demonstrated for the first time on fowl; fertilized eggs were obtained after insemination of chickens with sperm stored at –79 °C for one hour, but all the embryos died within 10-15 h after fertilisation [20]. Soviet scientists Milovanov V.K. (Doctor of biological Sciences) and Sokolovskaya I.I. (Doctor of biological Sciences Smirnov I.V) developed the method for cryoconservation of the semen of domestic animals which then served as a foundation for a wide range of practical applications of AI technology. In 1947, Sokolovskaya I.I. published this work in the journal "Proceedings of the Soviet Academy of Agricultural Science", in which, for the first time, she showed the ability of mammalian spermatozoa to maintain their viability after freezing/thawing and to produce viable offspring. Sixty-nine healthy offspring were born after insemination of rabbits with semen subjected to freezing in carbon dioxide vapor and subsequent thawing [21]. This was a scientific breakthrough that served as the basis for research on other farm animal species. The next major milestone was the use of glycerol as a cryoprotectant in the process of freezing and preserving the semen at low temperatures. Although most studies have attributed the cryoprotective role of glycerol to Christopher Polge [22], in 1937, Soviet scientists Bernstein A.D. and Petropavlovsky V.V. used glycerol to freeze the bull, ram, stallion, boar, and rabbit spermatozoa at –21 °C [23]. However, their work was published in Russian, and therefore, was not widely recognized. Using glycerol as a cryoprotectant after insemination with frozen-thawed semen, viable offspring were produced in chickens [24] and cattle [25] in 1951, and in pigs [26] and horses [27] in 1957. AI technology has been widely used in cattle breeding since the late 50s and early 60s, becoming the basis for the development of large-scale breeding [28, 29]. An additional technical advantage of AI technology is the development of a method for sorting spermatozoa carrying X-and Y-chromosomes [30, 31, 32], which is based on the measurement of DNA content in mammalian spermatozoa using flow cytometry [33]. Subsequently, this method was improved and numerous practical applications were identified [31]. Today, in countries with developed cattle breeding, AI is used in 100% of the dairy cattle population. The genetic potential of the best breeding bulls is replicated from several hundred thousand to more than a million offspring (http://www.holsteinusa.com, cited according 34), significantly increasing the degree of genetic gain.

The main milestones in the development of AI technology are summarized in Figure 1. AI technology has become the basis for the development of other ARTs, such as embryo transfer, in vitro embryo production, cloning, transgenesis, and GE.

Another important aspect is multi-replication of the genetic potential of highly productive cows. Relatively late puberty (12-13 months and older), single birth, and a relatively long period of pregnancy when using traditional AI technology ensures that the first offspring is produced in cows two years and older, and in the subsequent period (under optimal conditions), an average of one calf per year. The solution to this problem is highly relevant for the implementation of programs for the conservation of rare (small and gene-pool breeds) and unique (genetically modified animals) genetic resources. In this respect, the goal of ART development is to ensure that more offspring from a single female are produced as early as possible.

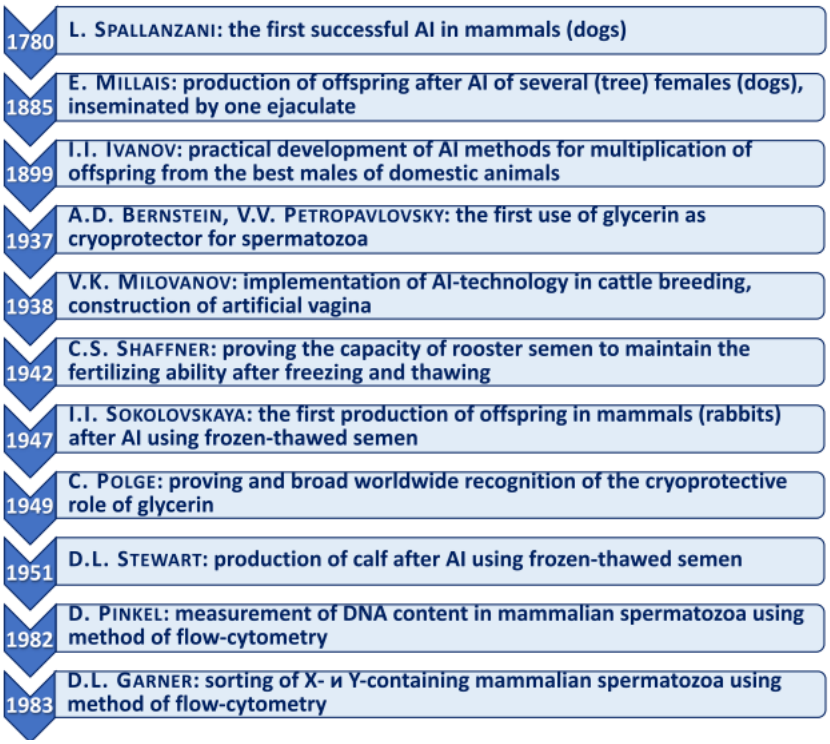

Fig. 1. The main stages of development of artificial insemination (AI) technology. L. Spallanzani [11], W. Heape [12], E. Millais [14], I.I. Ivanov [17], A.D. Bernstein, V.V. Petropavlovsky [23], V.K. Milovanov [19], C.S. Shaffner [20], I.I. Sokolovskaya [21], Polge C. et al. [22], Stewart D. et al. [25], Pinkel D. et al. [33], Garner D.E. et al. [30].

The first such technology was embryo transfer (ET), which includes the induction of superovulation in donor cows through hormonal treatment, artificial insemination, followed by embryo washing (on days 6-7 after AI), and embryo transfer to recipient cows [review 35, 36]. The first ET calf after surgical transplantation of a 5-day-old embryo obtained at a slaughterhouse was born in 1951 in the United States [37]. At the early stages, embryo recovery and transplantation were performed surgically, which limited the practical use of ET. In 1976, non-surgical embryo recovery was performed for the first time [38], and in the early 80s, non-surgical embryo transfer was performed in cows [39], which allowed these operations to be performed on the farm. The main goal of early ET programs was to distribute desirable phenotypes in herds. In 1988, scientists at the University of Guelph proposed the concept of multiple ovulation and embryo transfer (MOET) [40] to increase the genetic potential of herds. It was shown that the establishment of nucleus herds and "juvenile MOET" in the offspring of heifers can almost double the degree of genetic progress compared to traditional schemes of progeny testing evaluation. According to the International Embryo Transfer Society (IETS, http://www.iets.org/comm_data.asp) from 1997 to 2005 there was a progressive increase in the number of MOET embryos, i.e., approximately 450 thousand to almost 800 thousand per year, after which from 2005 to 2013 the production of embryos was stabilized at 700-800 thousand embryos per year. From 2014-2016, embryo production decreased to about 610-660 thousand, mainly due to an increase in the number of embryos obtained in vitro [cited according 41].

The main disadvantage of ET technology is the need for hormonal treatment: (1) it is known that not all donors respond equally well to hormonal stimulation; (2) the effectiveness of superovulation with each subsequent hormonal

treatment decreases (as a rule, the effective response to hormonal stimulation in cows is observed during 2-4 consecutive treatments); (3) a break of 2-3 months between hormonal treatments is required, which increases the cost of maintaining the donor cows. In addition, it is impossible to obtain embryos in cases of oviduct pathology [42, 43].

The next scientific breakthrough in the development of ART was in vitro embryo production (IVP) [review 41]. Classical IVP technology involves obtaining oocytes from the ovaries of cows by follicle aspiration, followed by in vitro maturation (IVM), in vitro fertilisation (IVF), and in vitro development of embryos (IVD) to stages suitable for transplantation or freezing (usually, late morula and blastocyst). The first calves resulting from in vitro fertilisation of the ovulated oocytes maturated in vivo were born in 1981 [44]. The first calves produced exclusively by IVP, including IVM, IVF, and IVD, were reported in the late 80s [45]. Initially, IVP embryos were produced using oocytes recovered from the ovaries of cows after slaughter (post-mortem), which limited the use of this technology for the genetic improvement of cattle.

Integration of IVP technology into programs for the genetic improvement of livestock began with the development of Ovum-Pick-Up (OPU), a method for the non-invasive recovery of oocytes [reviews 46, 47] from antral follicles in live animals [48-50]. In vivo retrieval of cow oocytes was first performed by Canadian scientists using endoscopy through the right paralumbar fossa [51]. In 1987, transcutaneous aspiration of cow follicles under ultrasound control was proposed in Denmark [52]. The next step was the development of a method for the retrieval of cow oocytes by ultrasound-assisted transvaginal aspiration of follicles, in 1988 by Dutch scientists [53]. This method has superseded all the methods mentioned above and is currently the standard method for obtaining of cow oocytes. Unlike MOET, OPU does not interfere with the normal reproduction and production cycle of the donor (no long-term negative effects on the fertility of donor cows were observed, even after OPU was performed twice a week for more than a year [54, 55]). Any female between three months and six months of pregnancy and shortly after calving (2-3 weeks) can become a suitable donor [47]. Currently, OPU is a practical alternative to the traditional MOET strategy [48, 49] and is increasingly used in commercial programs around the world [50, 56]. Although there are significant differences between individual donors, the joint use of OPU/IVP can result in the production of more than 50 calves per donor cow per year. Therefore, Kruip et al. [57] performed OPU twice a week for five months and obtained an average of 340 oocytes and 54 suitable embryos from one cow. In 2016, the number of IVP cow embryos produced in the world was more than 600 thousand and for the first time exceeded the production of MOET embryos (IETS, cited according 41). Considering the important role of OPU in the development of highly advanced genetic technologies, such as embryonic breeding [58] and genome editing [review 7], we focused on the research areas for improving OPU technology in more detail.

To increase the efficiency of OPU technology, studies have been conducted to identify factors that affect the number and quality of the obtained oocytes. The original OPU technology does not include hormonal stimulation, which limits the number of oocytes received. In this regard, various schemes of hormonal stimulation of donor cows using gonadotropins of the placenta (for example, pregnant mare serum gonadotropin, PMSG) and pituitary origin (for example, follicle-stimulating hormone, FSH) are used to obtain more oocytes per session [48, 59, 60]. We performed a study on the effect of hormonal stimulation using FSH on OPU in Simmental heifers. FSH treatment resulted in an average 3.2-fold increase

(from 4.5 to 14.6) in the number of ultrasound-visible follicles (3 mm or more in diameter), as well as the number of recovered cumulus oocyte complexes (COCs) per session (from 2.4 to 7.7). At the same time, we did not find any differences in the quality of COCs obtained with or without hormonal stimulation [61].

Along with the advantages, using hormonal stimulation for OPU has some unresolved key issues. The prolonged use of exogenous hormones can disrupt the endocrine system of the donors, which can lead to infertility. Responses of donor to hormonal stimulation are different: when using FSH, the number of oocytes obtained per session varied in different animals from 0 to 26 [62]. Even the same donor may show different reactions in different sessions, which leads to unstable results. In this regard, it is ideal to use hormones for a short period, leaving time for regulation and rehabilitation of the endocrine system [47).

Other factors that affect the effectiveness of OPU are time regimen (frequency of OPU sessions), technical and technological parameters of OPU, individual characteristics of donors (breed, age, reproductive phase, and individual response), availability of necessary nutrients in the diet [63], climatic conditions [64, 65], and operator experience [review 47].

The classic OPU procedure (without hormonal stimulation), in most cases, involves performing a puncture twice a week (2/w). The choice in favor of the 2/w regimen is due to an increase in the frequency of follicular waves, a delay in the estrous cycle, follicle maturation, and ovulation. Animals subjected to OPU in the 2/w regimen come to a so-called paraphysiological state in which follicular waves are independent of the estrous cycle [57]. When using this regimen, the dominant follicle does not develop, since all visible follicles are aspirated during the OPU process. When OPU is performed once a week (1/w) and less often, in most cases, the dominant follicle develops, which leads to regression and degeneration of subordinate follicles.

Comparative analysis of OPU in 1/w and 2/w regimens did not reveal differences in the number of aspirated follicles, recovered oocytes, and blastocysts obtained on the 7th day of cultivation, per cow per session. However, on a weekly basis, all three parameters were significantly higher for the 2/w regimen compared to 1/w [66-68). We studied the effect of two different time regimens on the OPU in Simmental heifers in terms of the quantity and quality of oocytes obtained [69]. On average, 4.4 oocytes were received from each donor per session using both regimens. We found a significant 1.2-fold increase ($p < 0.05$) in the rate of OPU oocytes of good quality characterized by normal morphology when performing the 2/w regimen (65.7±4.0% of the total number of recovered oocytes) compared to the 1/w regimen (53.6±3.0%). Considering the values of the rate of oocyte maturation (74.0%), the rate of cleavage of fertilized oocytes (on average 63.5%), the rate of development of embryos to the blastocyst stage (on average 16.7%), and the increase in the rate of good-quality oocytes compared to OPU sessions once a week, the 2/w regimen produced 2.5 times more embryos in the blastocyst stage from one donor for a certain period of time [69].

The influence of age and various physiological conditions on the effectiveness of OPU has been established. Rizos et al. [70] showed higher OPU performance in Holstein heifers than in cows: the total number of recovered oocytes was 4.7 vs. 2.8, respectively, including the number of oocytes of the 1st-2nd degree - 3.0 vs. 1.8. Significant differences in the cleavage rate of fertilized oocytes and blastocyst yield between heifers and cows were not observed [70].

The influence of the physiological state on the ability of OPU-oocytes to further develop has been established. In an experiment on Japanese Black cattle, it was shown that the cleavage rate of fertilized oocytes and their development to

the blastocyst stage, as well as survival after freezing, was higher for embryos obtained from oocytes recovered from pregnant cows than for embryos from non-pregnant cows [71].

Significant differences in the efficiency of OPU between the *Bos Taurus* and *Bos indicus* breeds (zebu cattle) have been revealed. Significantly more oocytes were obtained from *Bos indicus* donors [72, 73], mainly due to the larger population of follicles in the ovary. Between 18 and 25 oocytes were obtained from donors of Nelore zebu cattle bred in Brazil without the use of exogenous hormones or synchronisation protocols [74, 75]. A comparative study of the Holstein breed (*Bos Taurus*) and the Gir breed (*Bos indicus*) was performed by Pontes J.H.F. et al. [50]. The number of viable oocytes recovered per one OPU session in donor cows of the Holstein breed, the Gir breed, the 1/2 Holstein * 1/2 Gir and 1/4 Holstein * 3/4 Gir crosses was 8.0±2.7, 12.1±3.9, 24.3±4.7, and 16.8±5.0, respectively. The rate of IVP embryos obtained after insemination by sexed semen did not differ significantly between the groups and was 36-40% [50]. There were no noticeable differences in OPU efficiency between different *Bos taurus* cattle breeds. To predict the number of antral follicles in the ovaries of *Bos taurus* and *Bos indicus* cows and, consequently, the efficiency of OPU, measurement of the concentration of anti-muller hormone in blood plasma, which is produced by follicle cells during their maturation, can be used [76].

The sensitivity of ultrasound devices, the type (sector or linear), frequency of the probe used [57, 77], vacuum characteristics [78, 79, 80], the diameter and length of the slope of the needle [57, 81, 82], scrolling the needle inside the follicle during aspiration [80, 83], and removal of the dominant follicle are technical factors that affect the efficiency of OPU [66, 84].

Another possibility of obtaining oocytes from live cows is the laparoscopic collection of oocytes (L-OPU), which was first used in cattle in 1992 [85]. L-OPU has a number of advantages over the classical OPU procedure, including the choice of follicles for aspiration, the possibility of aspiration of follicles with a smaller diameter (2 mm or more), direct observation of the reproductive organs and ovary, visual control of the aspiration procedure, and reduced risk of ovarian damage. Comparative studies have shown that using the classical OPU technology, more oocytes of good quality were obtained and, as a result, a higher yield of embryos at the morula/blastocyst stage was achieved compared to L-OPU [86, 87]. L-OPU technology is used for obtaining oocytes from prepubertal females (aged 2 months and older), on which the use of classical OPU technology is impossible. Using L-OPU on heifers aged 2-6 months, 4.6 [85], 21.4 [88], and 42.6 oocytes [89] were obtained in one session. The use of prepubertal females with high breeding value as oocyte donors, selected based on the results of genomic evaluation, can reduce the generation interval and, as a result, increase the genetic progress [90]. However, for the practical application of this technology, it is necessary to improve the protocols for in vitro production of embryos using juvenile oocytes.

Reichenbach et al. [91] proposed a modification of the L-OPU method, in which access to the ovaries of cows is achieved through the vaginal fornix of cows. The procedure can be performed on animals under epidural anesthesia in less than 15 minutes, does not require surgery, and can be performed in the field.

Another scientific breakthrough in the development of ART as a basis for the development of advanced genetic technologies in cattle was the successful somatic cell nuclear transfer (SCNT). SCNT is a method in which the somatic cell nucleus is transferred to an enucleated oocyte to produce a new individual that is genetically identical to the somatic cell donor [reviews 92-94]. The

production of calves by somatic cloning was first reported in 1993 [95]. Inner cell mass (ICM) cells obtained from blastocysts and cultured from six to 100 days before use were used for cloning. In 1998, the first calves obtained by SCNT using differentiated somatic cells (foetal fibroblasts) were reported [96].

Thus, over a century-old history, various technologies have been developed and implemented into practice in cattle breeding (Table 1), which became the basis for the development of effective technologies for the genetic improvement of cattle, including genomic selection [3, 97].

1. Milestones in the development of assisted reproductive technologies that became the basis for the development of genetic technologies in cattle breeding

Events	Year
I.I. Ivanov: production of offspring after artificial insemination of cows	1899
D. STEWART: birth of calf after insemination by frozen-thawed semen	1951
E.L. WILLETT: birth of first ET calf after surgical transfer of 5-day embryos	1951
R.P. ELSDEN: non-surgical recovery of cows' embryos	1976
R.F. ROWE: non-surgical transfer of cows' embryos	1980
B.G. BRACKETT: birth of calf after *in vitro* fertilization of the oocyte, matured *in vivo*	1981
K. GOTO: birth of calf, produced exclusively from IVP embryo, including IVM, IVF and IVD	1988
C. SMITH: MOET to improve the genetic potential of herds	1988
M.C. PIETERSE: recovery of oocytes from lived animals using ultrasound-guided transvaginal follicular aspiration (Ovum-Pick-Up)	1988
M. SIMS, N.L. FIRST: first birth of calves after SCNT using ICM-cells, cultured *in vitro*, as donor cells	1993
X. VIGNON: first birth of calves after SCNT using differentiated somatic cells as donor cells	1998

N o t e. Ivanov I.I. [17], Stewart D. et al. [25], Willett E.L. et al. [37], Elsden R.P. et al. [38], Rowe R.F. et al. [39], Brackett B.G. et al. [44], Goto K. et al. [45], Smith C. et al. [40], Pieterse M.C. et al. [53 , Sims M., First N.L. [95], Vignon X. et al. [96]; ET — embryo transfer, IVP — in vitro production, IVM — in vitro maturation, IVF — in vitro fertilization, IVD — in vitro development, MOET — multiple ovulation and embryo transfer, SCNT — somatic cell nucleus transfer, ICM — inner cell mass.

The improvement of ART, including IVP and ET technologies, and their introduction into routine laboratory practice, initiated attempts to introduce genetic changes in early embryos of farm animals. At the initial stage of development of transgenic technologies, microinjection of a DNA solution of gene constructs into the pronucleus of zygotes was used for these purposes [reviews 5, 98, 99]. The efficiency of this method for generating transgenic mammals was initially demonstrated in mice [100]. Transgenic farm animals were first reported in 1985 by two laboratories in the United States [101] and Germany [102]. The first transgenic calves carrying the human lactoferrin gene under the control of the bovine alpha-S1-casein promoter were produced in 1991 [103]. In subsequent years, various genetic modifications in farm animals of different species, including cattle, were performed using the microinjection method [review 104]. The main disadvantage of microinjection is its very high labor intensity and low efficiency: (1) to produce a single transgenic calf, more than 1000 zygotes must be injected [105]; (2) only about 70% of transgenic founder animals are able to transmit the transgene to their offspring; and (3) of the obtained transgenic lines, only 50% have an expression level sufficient for subsequent practical use [106]. Due to the high material costs of producing transgenic animals by microinjection, the main goals of genetic modification of domestic animals were shifted from agricultural use to biomedical use, in which higher revenues from implementation are expected [106]. In the mid-90s of the XX century, the method of microinjection into the pronucleus of zygotes was almost completely replaced by the method of SCNT using genetically transformed cells (Fig. 2).

The advantages of SCNT in comparison with the method of microinjection are the ability to select donor cells of a certain sex and the in vitro preselection of cells that carry the specified genetic changes. As a result, 100% of

the produced offspring will have the desired sex and carry the necessary genetic modifications. Another advantage of SCNT in the subsequent application of the technology for agricultural purposes is the possibility of obtaining donor cells from highly productive animals as well as highly reliable prediction of the breeding value of future offspring using genomic estimation [6]. The disadvantages of this method include reduced viability of embryos obtained by SCNT, which is revealed by 60% higher embryonic mortality between 35 and 60 days of pregnancy compared to IVP embryos [108]. With the production of the first transgenic calf in 1998 carrying the reporter genes beta-galactosidase and neomycin [109], the SCNT method has been the dominant method for producing transgenic cattle for more than 15 years.

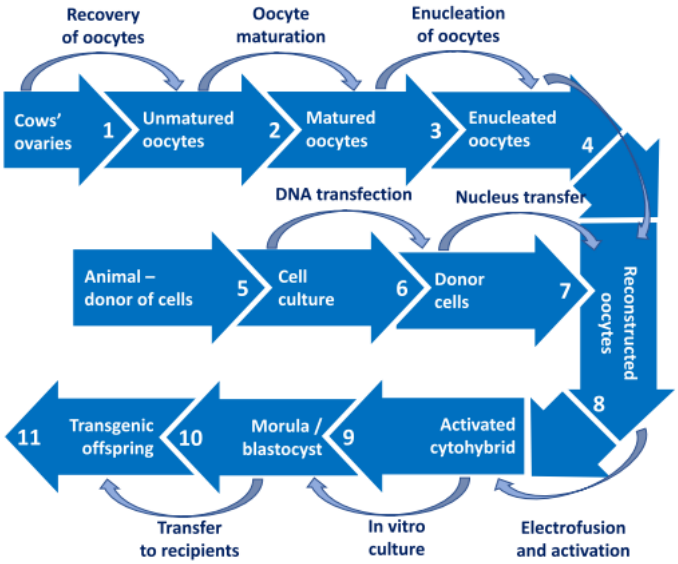

Fig. 2. Scheme for producing genetically modified animals using technology of somatic cell nuclear transfer (SCNT).

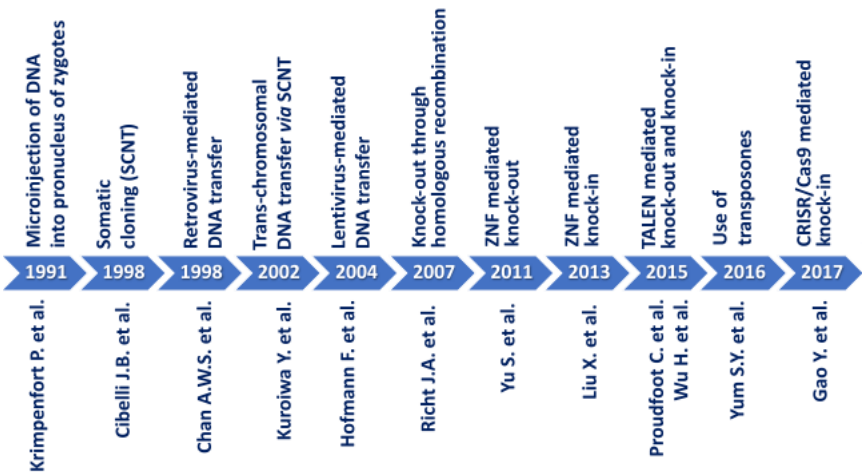

Fig. 3. Development of methods for genetic modification of cattle.
N o t e. Krimpenfort P. et al. [103], Cibelli J.B. et al. [109], Chan A.W.S. et al. [110), Kuroiwa Y. et al. [111], Hofmann F. et al. [112], Richt J.A. et al. [113], Yu S. et al. [114], Liu X. et al. [115], Proudfoot C. et al. [116], Wu H. et al. [117], Yum S.Y. et al. [118], Gao Y. et al. [119].

In combination with various ART, several different methods for the production of transgenic animals have been developed for over more than 30 years,

which have been successfully used to generate genetic GE cattle (Fig. 3). However, the use of transgenic technologies in cattle breeding has been limited until recently due to the relatively high cost of producing transgenic cattle, as well as owing to the lack of a reliable method that can ensure the introduction of specific genetic changes in the target genome regions with high efficiency [5, 6].

Further progress in the field of genetic engineering of domestic animals is associated with the development of technologies for GE, which enables the generation of targeted (site-specific) modifications of the genome [120]. Technologies involving DNA transposons [118] and site-specific nucleases, including ZNF "zinc finger" nucleases [114, 115], TALEN-transcription activator-like effector nuclease [116, 117], and CRISPR/Cas9-based systems are used as tools for GE in cattle [120]. Due to the relatively simple creation of gene constructs, the latter are becoming increasingly popular for GE in farm animals [review 7].

Two main methods are used to introduce targeted genetic changes in the germ lines of farm animals by GE, i.e., nucleus transfer of somatic cells (usually, embryonic fibroblasts) previously modified in vitro (see Fig. 2), and microinjection of the RNA form of gene constructs into the zygote. We discussed the advantages of the SCNT method above; however, SCNT is still not a routine procedure in many laboratories [121]. The microinjection method is relatively easy to perform. In contrast to the classical method of microinjection into the pronucleus of zygotes [101, 102], gene constructs are directly into the cytoplasm of zygotes. Although only a portion of animals derived from injected embryos carry the expected genetic changes, the microinjection method has been successfully implemented to create GE cattle [7]. In combination with the OPU/IVP technology—which allows a large number of zygotes to be obtained from parents with high breeding value—the method of microinjection can become the standard for use in programs for genetic improvement of cattle through GE.

Thus, for more than 100 years, significant progress has been made in the development of ART in cattle, and many of these techniques are now actively used in practical animal husbandry and have become the basis for the development of effective programs for genetic improvement of livestock, including genomic selection. Current research priorities are focused on ensuring further progress in cattle breeding by integrating GE technology into livestock breeding programs. ART will play a crucial role in this ambitious task.

REFERENCES

1. Cheng H., Clutter A., Cockett N., Ernst C., Fulton J.E., Liu J., Lunney J., Neibergs H., Purcell C., Smith T.P.L., Sonstegard T., Taylor J., Telugu B., Van Eenennaam A., Van Tassell C.P., Wells K. Genome to phenome: improving animal health, production, and well-being — a new USDA blueprint for animal genome research 2018-2027. *Frontiers in Genetics*, 2019, 10: 327 (doi: 10.3389/fgene.2019.00327).
2. *Federal'naya nauchno-tekhnicheskaya programma razvitiya geneticheskikh tekhnologii na 2019-2027 gody*. Utverzhdena Postanovleniem Pravitel'stva Rossiiskoi Federatsii ot 22 aprelya 2019 goda № 479 [Federal scientific and technical program for the development of genetic technologies for 2019-2027] (in Russ.).
3. VanRaden P.M., Van Tassell C.P., Wiggans G.R., Sonstegard T.S., Schnabel R.D., Taylor J.F., Schenkel F.S. Invited review: reliability of genomic predictions for North American Holstein bulls. *Journal of Dairy Science*, 2009, 92(1): 16-24 (doi: 10.3168/jds.2008-1514).
4. *Science breakthroughs to advance food and agricultural research by 2030. A consensus study report of the National Academies of Sciences, Engineering and Medicine*. The National Academies Press, Washington, DC, 2019 (doi: 10.17226/25059).
5. Yum S.Y., Youn K.Y., Choi W.J., Jang G. Development of genome engineering technologies in cattle: from random to specific. *Journal of Animal Science and Biotechnology*, 2018, 9: 16 (doi: 10.1186/s40104-018-0232-6).
6. Van Eenennaam A.L. Application of genome editing in farm animals: cattle. *Transgenic Research*, 2019, 28: 93-100 (doi: 10.1007/s11248-019-00141-6).

7. Zinovieva N.A., Volkova N.A., Bagirov V.A. Genome editing: current state of research and application to animal husbandry. *Applied Biochemistry and Microbiology*, 2019, 55(7): 711-721 (doi: 10.1134/S000368381907007X).
8. Foote R.H. The history of artificial insemination: selected notes and notables. *Journal of Animal Science*, 2002, 80(2): 1-10.
9. Saacke R.G. AI: a historical perspective. *Proc. of the 24th Technical Conference on Artificial insemination and reproduction*. Milwaukee, WI, USA, 2012: 138-150.
10. Lonergan P. Review: Historical and futuristic developments in bovine semen technology. *Animal*, 2018, 12(S1): s4-s18 (doi: 10.1017/S175173111800071X).
11. Spallanzani L. *Experiences pour servir a l'liistoire de la generation des animaux et des plantes*. Geneve, 1786.
12. Heape W. The artificial insemination of mammals and subsequent possible fertilisation or impregnation of their ova. *Proceedings of the Royal Society of London*, 1897, 61(369-377): 52-63 (doi: 10.1098/rspl.1897.0012).
13. Home E. An account of the dissection of an hermaphrodite dog. To which are prefixed, some observations on hermaphrodites in general. By Everard Home, Esq. F. R. S. *Philosophical Transactions of the Royal Society*, 1799, 89: 157-178. Available: https://www.jstor.org/stable/107031. Accessed: 21.04.2020.
14. Millais E. Influence with special reference to that of sire. In: *The Dog Owners' Annual for 1894*. London, Dean, 1894: 153.
15. Herman H.A. *Improving cattle by the millions: NAAB and the development and worldwide application of artificial insemination*. University of Missouri Press, Columbia, 1981.
16. Walters E.M., Benson J.D., Woods E.J., Critser J.K. The history of sperm cryopreservation importance of sperm cryopreservation. In: *Sperm banking: theory and practice*. A.A. Pacey, M.J. Tomlinson (eds.). Cambridge University Press, 2009.
17. Ivanov I.I. *Arkhiv biologicheskikh nauk*, 1906, 12(4-5): 376-509 (in Russ.).
18. Ivanoff E.I. On the use of artificial insemination for zootechnical purposes in Russia. *The Journal of Agricultural Science*, 1922, 12(3): 244-256 (doi: 10.1017/s002185960000530x).
19. Milovanov V.K. *Iskusstvennoe osemenenie sel'skokhozyaistvennykh zhivotnykh* [Artificial insemination of farm animals]. Moscow, 1938 (in Russ.).
20. Shaffner C.S. Longevity of fowl spermatozoa in frozen condition. *Science*, 1942, 96(2493): 377 (doi: 10.1126/science.96.2493.337).
21. Sokolovskaya I.I. *Doklady VASKHNIL*, 1947, 6: 21-23 (in Russ.).
22. Polge C., Smith A.U., Parkes A.S. Revival of spermatozoa after vitrification and dehydration at low temperatures. *Nature*, 1949, 164: 666 (doi: 10.1038/164666a0).
23. Bernshtein A.D., Petropavlovskii V.V. *Byulleten' eksperimental'noi biologii i meditsiny*, 1937, 1: 21-25 (in Russ.).
24. Polge C. Functional survival of fowl spermatozoa after freezing at –79 °S. *Nature*, 1951, 167: 949-950 (doi: 10.1038/167949b0).
25. Smith A.U., Polge C. Storage of bull spermatozoa at low temperatures. *Veterinary Record*, 1950, 62: 115-116.
26. Hess E.A., Teague H.S., Ludwick T.M., Martig R.C. Swine can be bred with frozen semen. *Ohio Farm Home Res.*, 1957, 42: 100
27. Barker C.A.V., Grandier J.C.C. Pregnancy in a mare resulted from frozen epididymal spermatozoa. *Can. J. Comp. Med. Vet. Sci.*, 1957, 21(2): 47-51.
28. Milovanov V.K., Sokolovskaya I.I. *Vestnik sel'skokhozyaistvennoi nauki*, 1980, 12: 122-134 (in Russ.).
29. Ernst L.K., TSalitis A.A. *Krupnomasshtabnaya selektsiya v skotovodstve* [Large-scale livestock breeding]. Moscow, 1982 (in Russ.).
30. Garner D.L., Gledhill B.L., Pinkel D., Lake S., Stephenson D., Van Dilla M.A., Johnson L.A. Quantification of the X- and Y-chromosome-bearing spermatozoa of domestic animals by flow cytometry. *Biology of Reproduction*, 1983, 28(2): 312-321 (doi: 10.1095/biolreprod28.2.312).
31. Seidel G.E. Jr. Update on sexed semen technology in cattle. *Animal*, 2014, 8(s1): 160-164 (doi: 10.1017/S1751731114000202).
32. Rath D., Barcikowski S., de Graaf S., Garrels W., Grossfeld R., Klein S., Knabe W., Knorr C., Kues W., Meyer H., Michl J., Moench-Tegeder G., Rehbock C., Taylor U., Washausen S. Sex selection of sperm in farm animals: status report and developmental prospects. *Reproduction*, 2013, 145(1): R15-R30 (doi: 10.1530/REP-12-0151).
33. Pinkel D., Lake S., Gledhill B.L., Van Dilla M.A., Stephenson D., Watchmaker G. High resolution DNA content measurements of mammalian sperm. *Cytometry*, 1982, 3(1): 1-9 (doi: 10.1002/cyto.990030103).
34. Zinovieva N.A. Haplotypes affecting fertility in Holstein cattle. *Sel'skokhozyaistvennaya Biologiya* [*Agricultural Biology*], 2016, 51(4): 423-435 (doi: 10.15389/agrobiology.2016.4.423eng).
35. Betteridge K.J. A history of farm animal embryo transfer and some associated techniques. *Animal Reproduction Science*, 2003, 79(3-4): 203-244 (doi: 10.1016/S0378-4320(03)00166-0).

36. Mapletoft R.J. History and perspectives on bovine embryo transfer. *Animal Reproduction*, 2013, 10(3): 168-173
37. Willett E.L., Black W.G., Casida L.E., Stone W.H., Buckner P.J. Successful transplantation of a fertilized bovine ovum. *Science*, 1951, 113(2931): 247 (doi: 10.1126/science.113.2931.247).
38. Elsden R.P., Hasler J.F., Seidel G.E. Jr. Non-surgical recovery of bovine eggs. *Theriogenology*, 1976, 6(5): 523-532 (doi: 10.1016/0093-691X(76)90120-5).
39. Rowe R.F., Del Campo M.R., Critser J.K., Ginther O.J. Embryo transfer in cattle: nonsurgical transfer. *Am. J. Vet. Res.*, 1980, 41(7): 1024-1028.
40. Smith C. Applications of embryo transfer in animal breeding. *Theriogenology*, 1988, 29(1): 203-212 (doi: 10.1016/0093-691X(88)90040-4).
41. Ferré L., Kjelland M., Strøbech L., Hyttel P., Mermillod P., Ross P. Recent advances in bovine in vitro embryo production: reproductive biotechnology history and methods. *Animal*, 2020, 14(5): 991-1004 (doi: 10.1017/S1751731119002775)
42. Ernst L.K., Sergeev N.I. *Transplantatsiya embrionov sel'skokhozyaistvennykh zhivotnykh* [Transplantation of farm animal embryos]. Moscow, 1989 (in Russ.).
43. Prokof'ev M.I. *Regulyatsiya vosproizvodstva krupnogo rogatogo skota* [Regulation of cattle reproduction]. Moscow, 1989 (in Russ.).
44. Brackett B.G., Bousquet D., Boice M.L., Donawick W.J., Evans J.F., Dressel M.A. Normal development following in vitro fertilization in the cow. *Biology of Reproduction*, 1982, 27(1): 147-158 (doi: 10.1095/biolreprod27.1.147).
45. Goto K., Kajihara Y., Kosaka S., Koba M., Nakanishi Y., Ogawa K. Pregnancies after co-culture of cumulus cells with bovine embryos derived from in-vitro fertilization of in-vitro matured follicular oocytes. *Journal of Reproduction and Fertility*, 1988, 83(2): 753-758 (doi: 10.1530/jrf.0.0830753).
46. Boni R. Ovum pick-up in cattle: a 25 years retrospective analysis. *Animal Reproduction*, 2012, 9(3): 362-369.
47. Qi M., Yao Y., Ma H., Wang J., Zhao X., Liu L., Tang X., Zhang L., Zhang S., Sun F. Transvaginal ultrasound guided Ovum Pick-up (OPU) in cattle. *Journal of Biomimetics Biomaterials and Tissue Engineering*, 2013, 18: 118 (doi: 10.4172/1662-100X.1000118).
48. Kruip T.A.M., Pieterse M.C., van Beneden T.H., Vos P.L., Wurth Y.A., Taverne M.A. A new method for bovine embryo production: a potential alternative to superovulation. *Veterinary Record*, 1991, 128(9): 208-210 (doi: 10.1136/vr.128.9.208).
49. Bousquet D., Twagiramungu H., Morin N., Brisson C., Carboneau G., Durocher J. In vitro embryo production in the cow: an effective alternative to the conventional embryo production approach. *Theriogenology*, 1999, 51(1): 59-70 (doi: 10.1016/S0093-691X(98)00231-3).
50. Pontes J.H.F., Silva K.C.F., Basso A.C., Rigo A.G., Ferreira C.R., Santos G.M.G., Sanches B.V., Porcionato J.P., Vieira P.H., Faifer F.S., Sterza F.A., Schenk J.L., Seneda M.M. Large-scale in vitro embryo production and pregnancy rates from *Bos taurus*, *Bos indicus*, and indicus-taurus dairy cows using sexed sperm. *Theriogenology*, 2010, 74(8): 1349-1355 (doi: 1010.1016/j.theriogenology.2010.06.004).
51. Lambert R.D., Bernard C., Rioux J.E., Bйland R., D'Amours D., Montreuil A. Endoscopy in cattle by the paralumbar route: technique for ovarian examination and follicular aspiration. *Theriogenology*, 1983, 20(2): 149-161 (doi: 10.1016/0093-691X(83)90210-8).
52. Callesen H., Greve T., Christensen F. Ultrasonically guided aspiration of bovine follicular oocytes. *Theriogenology*, 1987, 27(1): 217 (doi: 10.1016/0093-691X(87)90094-X).
53. Pieterse M.C., Kappen K.A., Kruip T.A.M., Taverne M.A.M. Aspiration of bovine oocytes during transvaginal ultrasound scanning of the ovaries. *Theriogenology*, 1988, 30(4): 751-762 (doi: 10.1016/0093-691X(88)90310-X).
54. Galli C., Crotti G., Notari C., Turini P., Duchi R., Lazzari G. Embryo production by ovum pick up from live donors. *Theriogenology*, 2001, 55(6): 1341-1357 (doi: 10.1016/S0093-691X(01)00486-1).
55. Chastant-Maillard S., Quinton H., Lauffenburger J., Cordonnier-Lefort N., Richard C., Marchal J., Mormede P., Renard J.P. Consequences of transvaginal follicular puncture on well-being in cows. *Reproduction*, 2003, 125(4): 555-563 (doi: 10.1530/rep.0.1250555).
56. Faber D.C., Molina J.A., Ohlrichs C.O., Vander Zwaag D.F., Ferre L.B. Commercialization of animal biotechnology. *Theriogenology*, 2003, 59(1): 125-138 (doi: 10.1016/S0093-691X(02)01264-5).
57. Kruip T.A.M., Boni R., Wurth Y.A., Roelofsen M.W.M., Pieterse M.C. Potential use of ovum pick-up for embryo production and breeding in cattle. *Theriogenology*, 1994, 42(4): 675-683 (doi: 10.1016/0093-691X(94)90384-U).
58. Wu B., Zan L., Quan F., Wang H. A novel discipline in embryology — animal embryo breeding. In: *New discoveries in embryology*. B. Wu (ed.). IntechOpen Limited, London, 2015: Ch. 8 (doi: 10.5772/61299).
59. Chaubal S.A., Ferre L.B., Molina J.A., Faber D.C., Bols P.E., Rezamand P., Tian X., Yang X. Hormonal treatments for increasing the oocyte and embryo production in an OPU-IVP system. *Theriogenology*, 2007, 67(4): 719-728 (doi: 10.1016/j.theriogenology.2006.07.022).

60. Sendag S., Cetin Y., Alan M., Hadeler K.G., Niemann H. Effects of eCG and FSH on ovarian response, recovery rate and number and quality of oocytes obtained by ovum pick-up in Holstein cows. *Animal Reproduction Science*, 2008, 106(1-2): 208-214 (doi: 10.1016/j.anireprosci.2008.01.007).
61. Chinarov R.Yu., Taradainik N.P., Taradainik T.E., Singina G.N., Pozyabin S.V. V sbornike: *Nauchnye trudy uchebno-metodicheskoi i nauchno-prakticheskoi konferentsii, posvyashchennoi 100-letiyu so dnya osnovaniya FGBOU VO MGAVMiB — MVA im. K.I. Skryabina «Aktual'nye problemy veterinarnoi meditsiny, zootekhnii i biotekhnologii»* [In: Scientific works of conference "Actual problems of veterinary medicine, livestock and biotechnology" dedicated to the 100th anniversary of Skryabin Moscow State Academy of Veterinary Medicine and Biotechnology]. Moscow, 2019: 377-378 (in Russ.).
62. De Roover R., Bols P.E.J., Genicot G., Hanzen Ch. Characterisation of low, medium and high responders following FSH stimulation prior to ultrasound- guided transvaginal oocyte retrieval in cows. *Theriogenology*, 2005, 63(7): 1902-1913 (doi: 10.1016/j.theriogenology.2004.08.011).
63. Leroy J.L.M.R., Van Soom G., Opsomer G., Goovaerts I.G.F., Bols P.E.J. Reduced fertility in high-yielding dairy cows: Are the oocyte and embryo in danger? Part II. Mechanisms linking nutrition and reduced oocyte and embryo quality in high-yielding dairy cows. *Reproduction in Domestic Animals*, 2008, 43(5): 623-632 (doi: 10.1111/j.1439-0531.2007.00961.x).
64. Ferreira R.M., Ayres H., Chiaratti M.R., Ferraz M.L., Araújo A.B., Rodrigues C.A., Watanabe Y.F., Vireque A.A., Joaquim D.C., Smith L.C., Meirelles F.V., Baruselli P.S. The low fertility of repeat-breeder cows during summer heat stress is related to a low oocyte competence to develop into blastocysts. *Journal of Dairy Science*, 2011, 94(5): 2383-2392 (doi: 10.3168/jds.2010-3904).
65. Ferreira R.M., Chiaratti M.R., Macabelli C.H., Rodrigues C.A., Ferraz M.L., Watanabe Y.F., Smith L.C., Meirelles F.V., Baruselli P.S. The infertility of repeat-breeder cows during summer is associated with decreased mitochondrial DNA and increased expression of mitochondrial and apoptotic genes in oocytes. *Biology of Reproduction*, 2016, 94(66): 1-10 (doi: 10.1095/biolreprod.115.133017).
66. Chaubal S.A., Molina J.A., Ohlrichs C.L., Ferre L.B., Faber D.C., Bols P.E., Riesen J.W., Tian X., Yang X. Comparison of different transvaginal ovum pick-up protocols to optimise oocyte retrieval and embryo production over a 10-week period in cows. *Theriogenology*, 2006, 65(8): 1631-1648 (doi: 10.1016/j.theriogenology.2005.07.020).
67. Lopes A.S., Martinussen T., Greve T., Callesen H. Effect of days post-partum, breed and ovum pick-up scheme on bovine oocyte recovery and embryo development. *Reproduction in Domestic Animals*, 2006, 41(3): 196-203 (doi: 10.1111/j.1439-0531.2006.00683.x).
68. Li F., Chen X., Pi W., Liu C., Shi Z. Collection of oocytes through transvaginal ovum pick-up for in vitro embryo production in Nanyang Yellow cattle. *Reproduction in Domestic Animals*, 2007, 42(6): 666-670 (doi: 10.1111/j.1439-0531.2006.00842.x).
69. Chinarov R.Yu., Lukanina V.A., Singina G.N., Taradainik N.P. *Dostizheniya nauki i tekhniki APK*, 2020, 34(2): 57-60 (doi: 10.24411/0235-2451-2020-10212) (in Russ.).
70. Rizos D., Burke L., Duffy P., Wade M., Mee J.F., O'Farrell K.J., Macsiurtain M., Boland M.P., Lonergan P. Comparisons between nulliparous heifers and cows as oocyte donors for embryo production in vitro. *Theriogenology*, 2005, 63(3): 939-949 (doi: 10.1016/j.theriogenology.2004.05.008).
71. Takuma T., Sakai S., Ezoe D., Ichimaru H., Jinnouchi T., Kaedei Y., Nagai T., Otoi T. Effects of season and reproductive phase on the quality, quantity and developmental competence of oocytes aspirated Japanese Black cows. *Journal of Reproduction and Development*, 2010, 56(1): 55-59 (doi: 10.1262/jrd.09-071h).
72. Guerreiro B.M., Batista E.O., Vieira L.M., Sá Filho M.F., Rodrigues C.A., Castro Netto A., Silveira C.R., Bayeux B.M., Dias E.A., Monteiro F.M., Accorsi M., Lopes R.N., Baruselli P.S. Plasma anti-mullerian hormone: an endocrine marker for in vitro embryo production from *Bos taurus* and *Bos indicus* donors. *Domestic Animal Endocrinology*, 2014, 49: 96-104 (doi: 10.1016/j.domaniend.2014.07.002).
73. Gimenes L.U., Ferraz M.L., Fantinato-Neto P., Chiaratti M.R., Mesquita L.G., Sá Filho M.F., Meirelles F.V., Trinca L.A., Renny F.P., Watanabe Y.F., Baruselli P.S. The interval between the emergence of pharmacologically synchronized ovarian follicular waves and ovum pickup does not significantly affect in vitro embryo production in *Bos indicus*, *Bos taurus*, and *Bubalus bubalis*. *Theriogenology*, 2015, 83(3): 385-393 (doi: 10.1016/j.theriogenology.2014.09.030).
74. Thibier M. Stabilization of numbers of in vivo collected embryos in cattle but significant increases of in vitro bovine produced embryos in some parts of the world. *IETS Embryo Transfer Society Newsletter*, 2004, 22: 12-19.
75. Rubin K.C.P., Pontes J.H.F., Nonato-Junior I., Ereno-Junior J.C., Pansard H., Seneda M. Influência do grau de sangue Nelore na produçro in vivo de oycitos. *Acta Scientiae Veterinariae*, 2005, 33: 183.
76. Batista E.O.S., Macedo G.G., Sala R.V., Ortolan M., Sá Filho M.F., Del Valle T.A., Jesus E.F., Lopes R., Renny F.P., Baruselli P.S. Plasma antimullerian hormone as a predictor of ovarian antral follicular population in *Bos indicus* (Nelore) and *Bos taurus* (Holstein) heifers. *Reproduction*

in Domestic Animals, 2014, 49(3): 448-452 (doi: 10.1111/rda.12304).
77. Bols P.E., Leroy J.L., Vanholder T., Van Soom A. A comparison of a mechanical sector and a linear array transducer for ultrasound-guided transvaginal oocyte retrieval (OPU) in the cow. *Theriogenology*, 2004, 62(5): 906-914 (doi: 10.1016/j.theriogenology.2003.12.016).
78. Ward F.A., Lonergan P., Enright B.P., Boland M.P. Factors affecting recovery and quality of oocytes for bovine embryo production in vitro using ovum pick-up technology. *Theriogenology*, 2000, 54(3): 433-446 (doi: 10.1016/s0093-691x(00)00360-5).
79. Manik R.S., Singla S.K., Palta P. Collection of oocytes through transvaginal ultrasound-guided aspiration of follicles in an Indian breed of cattle. *Animal Reproduction Science*, 2003, 76(3-4): 155-161 (doi: 10.1016/s0378-4320(02)00241-5).
80. Sasamoto Y., Sakaguchi M., Katagiri S., Yamada Y., Takahashi Y. The effects of twisting and type of aspiration needle on the efficiency of transvaginal ultrasound-guided ovum pick-up in cattle. *Journal of Veterinary Medical Science*, 2003, 65(10): 1083-1086 (doi: 10.1292/jvms.65.1083).
81. Bols P.E., Van Soom A., Ysebaert M.T., Vandenheede J.M., de Kruif A. Effects of aspiration vacuum and needle diameter on cumulus oocyte complex morphology and developmental capacity of bovine oocytes. *Theriogenology*, 1996, 45(5): 1001-1014 (doi: 10.1016/0093-691x(96)00028-3).
82. Bols P.E., Ysebaert M.T., Van Soom A., de Kruif A. Effects of needle tip bevel and aspiration procedure on the morphology and developmental capacity of bovine compact cumulus oocyte complexes. *Theriogenology*, 1997, 47(6): 1221-1236 (doi: 10.1016/s0093-691x(97)00102-7).
83. Fayrer-Hosken R.A., Caudle A.B. The laparoscope in follicular oocyte collection and gamete intrafallopian transfer and fertilization (GIFT). *Theriogenology*, 1991, 36(5): 709-725 (doi: 10.1016/0093-691x(91)90337-d).
84. Gradela A., Esper C.R., Matos S.P.M., Lanza J.A., Deragon L.A.G., Malheiros R.M. Dominant follicle removal by ultrasound guided transvaginal aspiration and superovulatory response in Nellore cows. *Arquivo Brasileiro de Medicina Veterinŏria e Zootecnia*, 2000, 52(1): 53-58.
85. Armstrong D.T., Holm P., Irvine B., Petersen B.A., Stubbings R.B., McLean D., Seamark R.F. Pregnancies and live birth from in vitro fertilization of calf oocytes collected by laparoscopic follicular aspiration. *Theriogenology*, 1992, 38(4): 667-678 (doi: 10.1016/0093-691x(92)90029-q).
86. Becker F., Kanitz W., Nurnberg G., Kurth J., Spitschak M. Comparison of repeated transvaginal ovum pick up in heifers by ultrasonographic and endoscopic instruments. *Theriogenology*, 1996, 46(6): 999-1007 (doi: 10.1016/S0093-691X(96)00264-6).
87. Santl B., Wenigerkind H., Schernthaner W., Mödl J., Stojkovic M., Prelle K., Holtz W., Brem G., Wolf E. Comparison of ultrasound-guided vs laparoscopic transvaginal ovum pick-up (OPU) in Simmental heifers. *Theriogenology*, 1998, 50(1): 89-100 (doi: 10.1016/s0093-691x(98)00116-2).
88. Baldassarre H., Currin L., Michalovic L., Bellefleur A.M., Gutierrez K., Mondadori R.G., Glanzner W.G., Schuermann Y., Bohrer R.C., Dicks N., Lopez R., Grand F.-X., Vigneault C., Blondinm P., Gourdon J., Bordignon V. Interval of gonadotropin administration for in vitro embryo production from oocytes collected from Holstein calves between 2 and 6 months of age by repeated laparoscopy. *Theriogenology*, 2018, 116: 64-70 (doi: 10.1016/j.theriogenology.2018.05.005).
89. Taneja M., Bols P.E., de Velde A.V., Ju J.C., Schreiber D., Tripp M.W., Yang X. Developmental competence of juvenile calf oocytes in vitro and in vivo: influence of donor animal variation and repeated gonadotropin stimulation. *Biology of Reproduction*, 2000; 62(1): 206-213 (doi: 10.1095/biolreprod62.1.206).
90. Lohuis M.M. Potential benefits of bovine embryo-manipulation technologies to genetic improvement programs. *Theriogenology*, 1995, 43(1): 51-60 (doi: 10.1016/0093-691X(94)00016-N).
91. Reichenbach H.D., Wiebke N.H., Modl J., Zhu J., Brem G. Laparoscopy through the vaginal fornix of cows for the repeated aspiration of follicular oocytes. *Veterinary Record*, 1994, 135(15): 353-356 (doi: 10.1136/vr.135.15.353).
92. Keefer C.L. Artificial cloning of domestic animals. *PNAS USA*, 2015, 112(29): 8874-8878 (doi: 10.1073/pnas.1501718112).
93. Bondioli K.R. Cloning of livestock by somatic cell nuclear transfer. In: *Animal Biotechnology 2*. H. Niemann, C. Wrenzycki (eds.). Springer, Cham, 2018: 1-20 (doi: 10.1007/978-3-319-92348-2_1).
94. Lopukhov A.V., Singina G.N., Zinovieva N.A. Biotechnological bases of the development of cloned pig embryos. *Vavilovskii Zhurnal Genetiki i Selektsii =Vavilov Journal of Genetics and Breeding*, 2019, 23(5): 527-533 (doi: 10.18699/VJ19.521).
95. Sims M., First N.L. Production of fetuses from totipotent cultured bovine inner cell mass cells. *Theriogenology*, 1993, 39(1): 313 (doi: 10.1016/0093-691X(93)90168-5).
96. Vignon X., Chesné P., Le Bourhis D., Heyman Y., Renard J.P. Developmental potential of bovine embryos reconstructed with somatic nuclei from cultured skin and muscle fetal cells. *Theriogenology*, 1998, 49: 392 (doi: 10.1016/S0093-691X(98)90745-2).
97. Sermyagin A.A., Belous A.A., Konte A.F., Philipchenko A.A., Ermilov A.N., Yanchukov I.N., Plemyashov K.V., Brem G., Zinovieva N.A. Genomic evaluation of bulls for daughters' milk traits in Russian Black-and-White and Holstein cattle population through the validation procedure. *Sel'skokhozyaistvennaya biologiya* [*Agricultural Biology*], 2017, 52(6): 1148-1156 (doi: 10.15389/agrobiology.2017.6.1148eng).
98. Serov O.L. *Vavilovskii zhurnal genetiki i selektsii*, 2013, 17(4/2): 1055-1064 (in Russ.).
99. Zinovieva N.A., Volkova N.A., Bagirov V.A., Brem G. Transgenic farm animals: the status of

research and prospects. *Russian Journal of Genetics: Applied Research*, 2016, 6(6): 657-668 (doi: 10.1134/S2079059716060101).
100. Gordon J.W., Scangos G.A., Plotkin D.J., Barbosa J.A., Ruddle F.H. Genetic transformation of mouse embryos by microinjection of purified DNA. *PNAS USA*, 1980, 77(12): 7380-7384 (doi: 10.1073/pnas.77.12.7380).
101. Hammer R., Pursel V., Rexroad J., Wall R.J., Bolt D.J., Ebert K.M., Palmiter R.D., Brinster R.L. Production of transgenic rabbits, sheep and pigs by microinjection. *Nature*, 1985, 315: 680-683 (doi: 10.1038/315680a0).
102. Brem G., Brenig B., Goodman H.M., Selden R.C., Graf F., Kruff B., Springman K., Hondele J., Meyer J., Winnacker E.-L. Production of transgenic mice, rabbits and pigs by microinjection into pronuclei. *Reproduction in Domestic Animals*, 1985, 20(4): 251-252 (doi: 10.1111/j.1439-0531.1985.tb00423.x).
103. Krimpenfort P., Rademakers A., Eyestone W., van der Schans A., van den Broek S., Kooiman P., Kootwijk E., Platenburg G., Pieper F., Strijker R., de Boer H. Generation of transgenic dairy cattle using 'in vitro' embryo production. *Biotechnology*, 1991, 9: 844-847 (doi: 10.1038/nbt0991-844).
104. Wall R.J. Pronuclear microinjection. *Cloning and Stem Cells*, 2001, 3(4): 209-220 (doi: 10.1089/15362300152725936).
105. Seidel G.E. Jr. Resource requirements for transgenic livestock research. *Journal of Animal Science*, 1993, 71(S. 3): 26-33 (doi: 10.2527/1993.71suppl_326x).
106. Eyestone W.H. Challenges and progress in the production of transgenic cattle. *Reproduction, Fertility and Development*, 1994, 6(5): 647-652 (doi: 10.1071/rd9940647).
107. Laible G. Production of transgenic livestock: overview of transgenic technologies. In: *Animal Biotechnology 2.* H. Niemann, C. Wrenzycki (eds.). Springer, Cham, 2018: 95-121 (doi: 10.1007/978-3-319-92348-2_6).
108. Galli C., Lagutina I., Lazzari G. Introduction to cloning by nuclear transplantation. *Cloning and Stem Cells*, 2003, 5(4): 223-232 (doi: 10.1089/153623003772032745).
109. Cibelli J.B., Stice S.L., Golueke P.J., Kane J., Jerry J., Blackwell C., Ponce de Leon A., Robl J.M. Cloned transgenic calves produced from non-quiescent fetal fibroblasts. *Science*, 1998, 280(5367): 1256-1258 (doi: 10.1126/science.280.5367.1256).
110. Chan A.W.S., Homan E.J., Ballou L.U., Burns J.C., Bremel R.D. Transgenic cattle produced by reverse-transcribed gene transfer in oocytes. *PNAS USA*, 1998, 95(24): 14028-14033 (doi: 10.1073/pnas.95.24.14028).
111. Kuroiwa Y., Kasinathan P., Choi Y.J., Naeem R., Tomizuka K., Sullivan E.J., Knott J.G., Duteau A., Goldsby R.A., Osborne B.A., Ishida I., Robl J.M. Cloned transchromosomic calves producing human immunoglobulin. *Nature Biotechnology*, 2002, 20(9): 889-94 (doi: 10.1038/nbt727).
112. Hofmann A., Zakhartchenko V., Weppert M., Sebald H., Wenigerkind H., Brem G., Wolf E., Pfeifer A. Generation of transgenic cattle by lentiviral gene transfer into oocytes. *Biology of Reproduction*, 2004, 71(2): 405-409 (doi: 10.1095/biolreprod.104.028472).
113. Richt J.A., Kasinathan P., Hamir A.N., Castilla J., Sathiyaseelan T., Vargas F., Sathiyaseelan J., Wu H., Matsushita H., Koster J., Kato S., Ishida I., Soto C., Robl J.M., Kuroiwa Y. Production of cattle lacking prion protein. *Nature Biotechnology*, 2007, 25: 132-138 (doi: 10.1038/nbt1271).
114. Yu S., Luo J., Song Z., Ding F., Dai Y., Li N. Highly efficient modification of beta-lactoglobulin (BLG) gene via zinc-finger nucleases in cattle. *Cell Research*, 2011, 21(11): 1638-1640 (doi: 10.1038/cr.2011.153).
115. Liu X., Wang Y., Guo W., Chang B., Liu J., Guo Z., Quan F., Zhang Y. Zinc-finger nickase-mediated insertion of the lysostaphin gene into the beta-casein locus in cloned cows. *Nature Communications*, 2013, 4(1): 2565 (doi: 10.1038/ncomms3565).
116. Proudfoot C., Carlson D.F., Huddart R., Long C.R., Pryor J.H., King T.J., Lillico S.G., Mileham A.J., McLaren D.G., Whitelaw C.B., Fahrenkrug S.C. Genome edited sheep and cattle. *Transgenic Research*, 2015, 24(1): 147-153 (doi: 10.1007/s11248-014-9832-x).
117. Wu H., Wang Y., Zhang Y., Yang M., Lv J., Liu J., Zhang Y. TALE nickase-mediated SP110 knock-in endows cattle with increased resistance to tuberculosis. *PNAS*, 2015, 112(13): E1530-E1539 (doi: 10.1073/pnas.1421587112).
118. Yum S.Y., Lee S.J., Kim H.M., Choi W.J., Park J.H., Lee W.W, Kim H.J., Bae S.H., Lee J.H., Moon J.Y., Lee J.H., Lee C.I., Son B.J., Song S.H., Ji S.M., Kim S.J., Jang G. Efficient generation of transgenic cattle using the DNA transposon and their analysis by next-generation sequencing. *Scientific Reports*, 2016, 6: 27185 (doi: 10.1038/srep27185).
119. Gao Y., Wu H., Wang Y., Liu X., Chen L., Li Q., Cui C., Liu X., Zhang J., Zhang Y. Single Cas9 nickase induced generation of NRAMP1 knock-in cattle with reduced off-target effects. *Genome Biology*, 2017, 18(1): 13 (doi: 10.1186/s13059-016-1144-4).
120. Bosch P., Forcato D.O., Alustiza F.E., Alessio A.P., Fili A.E., Olmos Nicotra M.F., Liaudat A.C., Rodríguez N., Talluri T.R., Kues W.A. Exogenous enzymes upgrade transgenesis and genetic engineering of farm animals. *Cellular and Molecular Life Sciences*, 2015, 72: 1907-1929 (doi: 10.1007/s00018-015-1842-1).
121. Singina G.N., Volkova N.A., Bagirov V.A., Zinov'eva N.A. Cryobanking of somatic cells in conservation of animal genetic resources: prospects and successes (review). *Sel'skokhozyaistvennaya biologiya* [*Agricultural Biology*], 2014, 6: 3-14 (doi: 10.15389/agrobiology.2014.6.3eng).