UDC 616-089.843]-003.93-576.54

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THE AGING: THEORY OF THE BODY STEM-SPACES DEPLETION

The review contains an analysis of basic information about the principles and methods of a new direction in the treatment of human diseases named as regenerative medicine, basic information on stem-spaces of organism, provides information on the depletion of stem cells resources in the aging, and presented authors own theory of the aging mechanisms.

Key words: *stem cell, stem-spaces, immune system replacement, aging, regenerative medicine.*

Evolution developed two main options for the completion of living cells — necrosis and apoptosis, which at the tissue level corresponds to the processes of proliferation and regeneration. Proliferation can be regarded as a kind of sacrifice while filling the defect of damaged tissue that occurs due to its substitution of connective tissue elements: maintaining the structural integrity, the body loses partly the function of the diseased organ, which determines the subsequent development of compensatory responses to hypertrophy or hyperplasia of structural-functional elements that remains undamaged. The duration of the compensation depends on the amount of structural lesions caused by alteration of factors or disease, then in most cases decompensation occurs, a sharp deterioration in the quality and reducing the length of human life. Physiological regeneration provides remodeling process, i. e. replacement of aging and dying by the mechanism of natural death (apoptosis) of cells with new ones derived from stem cell reserves of the human body. In the process of reparative regeneration also involved cells resource of stem-spaces, which however, has already mobilized in pathological conditions associated with disease or tissue damage that initiates cells death by necrosis mechanisms.

Methods of regenerative medicine aimed at stimulation of the recovery of lost functions — either by mobilizing the patient's own stem resources of the body, either through the introduction of allogenic cells material. One of these therapeutic methods is cells transplantation, known in history of medicine as a way to rejuvenate the aging organism. The term «cells therapy» is owned by a medicine and theology doctor Paul Niehans, who defined it as «a form of electoral influence whose goal is to develop the underdeveloped organ or organs which are incapable to self-regeneration». Beginning of stem cell therapy is calculated since 1931, when Niehans to rescue women from accidental removal of parathyroid glands, have successfully applied the introduction of parathyroid gland cells suspension of the ox. Further Niehans improved method of treatment by using for regenerative therapy cells of internal organs of sheep embryo — that is applied cells xenotransplantation. Among the most famous Niehans patients were Thomas Mann, who has lived for 80 years, Papa Piy XII — 82 years, Somerset Moaum — 91 years, Bernard Barukh — 95 years. Niehans himself died at the age of 89 years (Kurtzman J., Gordon Ph., 1976).

The current stage of regenerative medicine development is characterized by rapid progress in biotechnology, which is, above all, due to advances in the study of human embryonic stem cells (ESCs) biological properties (Snyder E.Y. et al., 1995; Gage F.H., 1998). It is now well known, such most important characteristics of cells of the early embryo as toti-, pluri- and multipotent. Totipotency, that is ability to recreate genetically programmed whole organism, possess cells of zygotes, blastomeres, and possibly embryonic

stem cells (cells of the inner mass of the blastocyst). Another group of potentially totipotent cells, which are formed at later stages of embryo development, represented the primary germ cells of embryonic germinative area (germinative tubercles). Pluripotency — the ability to differentiate into cells of tissues of any organ is inherent in embryonic cells of three germ layers — ecto-, meso- and endoderm. It is believed that multipotency, i.e., the ability to form any cell within the limit of single specialized tissue, properties of two cell types: the so-called mesenchymal stem cells, which are formed in the neural crest and are the precursors of all cells of the connective tissue framework of the body including cells of the neuroglia, as well as hematopoietic stem cells, giving rise to all blood cell lines. Besides, stem cells divided into bipotent and unipotent cells, in particular, the progenitor cells of myeloid, lymphoid, monocyte, and megakaryocyte hematogenous germs. The existence of unipotent stem cells clearly proved by the example of hepatocytes — the loss of much of the liver tissue is compensated by an intensive division of differentiated hepatocytes, but without the formation of new liver lobules (Civin C.I., 2000, Lukash L.L., Vasilovskaya S.V., 2001; Repin V.S., 2001a, b; Sukhikh G.T., Shtill A.A., 2002; Uryvaeva I.V., 2001; Malaytcev V.V. et al. 2002; McKay R., 2002).

In the literature of recent years an increasing number of reports on the plasticity of stem cells, considered not only as the ability of the latter to differentiate into various cell types at different stages of development, but also undergo dedifferentiation, transdifferentiation, and retrodifferentiation. That is allowed in principle the possibility of returning differentiated somatic cells at the stage of embryonic development, recapitulation (return) of pluripotency and its implementation in the re-differentiation to form cells of another type. In particular, reported that hematopoietic stem cells can undergo transdifferentiation with the formation of hepatocytes, endothelial cells and cardiomyoblasts (Morrison S.J. et al., 1997; Repin V.S., Sukhikh G.T., 1998; Vescovi A.L., 1999; Gryshchenko V.I., 2000; Schuldiner M. et al., 2000; Demin J.A., 2001; Korochkin L.I., 2001; Terekhov S.M. et al., 2001; Hawley R.G., Sobieski D.A., 2002).

Scientific debate on the division of stem cells in their plasticity continues, i.e. glossary and terminology for cell transplantation are in the process of development, that has directly practical significance, since on particular use of plastic properties and the ability of stem cells to differentiate into different cell lines based mostly of the regenerative medicine methods. To avoid misunderstanding it should be noted that in this article we use the classification in which stem cells are divided into two groups according to the periods of their functions in ontogenesis, as well as the ability to differentiate. To the stem cells of the first category relates the cells of preimplantation embryo and derivatives of presumptive germ cells. The second group divided to regional stem cells, which are a source of differentiated cells throughout the organism's life, including period of embryogenesis. On differentiation potential, stem cells divide into totipotential — capable of fully re-create organs and tissues of the body, pluripotential — giving rise to cells of the ecto-, endo- and mesodermal origin, and multipotential — derivatives which may have various types of cells in a single lineage of differentiation, as well as cells with more limited possible, that is bi- and mono (uni) potential (Civin C.I., 2000; Malaytcev V.V. et al. 2002; Hawley R.G., Sobieski D.A., 2002).

Above all, it is necessary to review question about the presence of stem-spaces in mammals and humans. One of them is well known — this is stem space of blood cells, localized in the adult bone marrow. And besides in the bone marrow are deposited not only hematopoietic stem and precursor cells of myelocytopoiesis, lymphocytopoiesis, erythrocytopoiesis and trombocytopoiesis, but also mesenchymal stem cells, multipotentcy of which is realized in the generation of connective tissue elements, hepatocytes, endothelial cells, myoblasts, osteocytes, chondrocytes, adipocytes and tendocytes (Sukhikh G.T. et al., 2002).

Hypothesis about the presence of blood cells single precursor was suggested by A.A. Maximov in 1909 year. Today established that the foundation of hematopoiesis constitutes of a single self-renewal multipotent hematopoietic stem cell. When its division formed primitive, and then committed progenitor cell from which formed morphologically recognizable porogenitor cells of different hematopoietic germs that ends with the release into the blood of mature erythrocytes, leukocytes, monocytes, lymphocytes, and platelets (Gluzman D.F. et al., 1998; Chertkov I.L., Drize N.I., 1998).

According to classical ideas, the embryogenesis of mammals is a natural change in the localization of hemopoiesis, which was originally performed in the yolk sac and then trav-

els to the liver, spleen, and finally to the bone marrow (Prindul G., 1998). However, new data obtained that in mammals, like in birds, together with the yolk sac, before the total closure of the vascular bed, in the body of the embryo (the so-called para-aortic splanchnopleura) appear hematopoietic cells, characterized as multipotent progenitor of T- and B- lymphocytes, granulocytes, megakaryocytes and macrophages (Godin I. et al., 1995; Schuldiner M. et al., 2000). Moreover, these multipotent progenitor cells phenotype proved to be very close to hematopoietic stem cells of adult animals bone marrow ($CD34^+c\text{-}kit^+$) (Sanchez M.J. et al., 1996).

Founded a new hemopoietic organ in the germ of mammals, in which hematopoiesis is detected simultaneously and independently from the extraembryonic yolk sac, raised the question which of these structures is a source of hematopoietic stem cells, providing definitive hematopoiesis. Analysis of contradictory information over some kind of consensus: hematopoietic cells of yolk sac in situ can differentiate only into primary red blood cells, but in the microenvironment of the newborn liver acquires the ability to repopulate hematopoietic organs and give rise initially to all hemopoiesis lineages of adult animal. On the other hand, the para-aortic splanchnopleura, denoted as an area of the aorta, gonads and mesonephros — AGM, initially contains hematopoietic stem cells, which are not in the yolk sac (Dieterlen-Lievre F., 1997).

The question of the biological sense of existence in the early mammalian embryogenesis hematopietic organs with similar functions remains unknown (Domaratskaya E.I. et al., 2001). However, we would like to draw attention to the fact that the primarily cells determinate to embryonic hematopoiesis, detected in mammals immediately after implantation (6 days) when the morphological features of hematopoietic differentiation and presumptive hematopietic organs still absent. At this stage disaggregated cells of mouse embryos are capable to repopulate hematopoietic organs of irradiated recipients and form red blood cells and lymphocytes, which differ from the host cells not only chromosomal markers T6, but the type of hemoglobin (Hollands P., 1987).

Stem space of the nervous system. The greatest number of publications devoted to the study of neural stem cells, which is not surprising, since the mere fact of multipotent cells detection in the central nervous system, apparently, violates the basic paradigm of neurology (Viktorov I.V., 2001). In the embryonic brain proliferating neuroepithelial stem cells comprise of germinal ventricular zone and subventricular region is the site of the primary migration of neuro- and glioblastes (Davis A.A., Temple S., 1994). In the mature brain walls of the lateral ventricles are formed by the layer of ependimyal cells that form a barrier separating brain tissue from cerebrospinal fluid fills the ventricles, and subependymal zone containing a reduced embryonic germinal tissue (Luskin M.B., 1993). Initially, data were obtained that in the wall of the lateral ventricles of the mature rat brain there is a population of proliferating cells and is a constant generation of progenitor cells that are able to follow migration and terminal differentiation into definitive neural and glial cells. In particular, it was found that the cells of rodents lateral ventricle subependymal zone give rise to a population of progenitor cells that migrate along the rostral migratory tract formed by the longitudinally oriented cells of astroglia. Reaching the olfactory bulb, migrating cells are embedded in the cell-grains layer, and become differentiated neurons of this structure (Lois C., Alvarez-Buylla A., 1993; Kuhn H.G., Svendsen C.N., 1999). Later migrating progenitor cells were detected in the rostral migratory tract of adult primates (Gould E. et al., 1999) and neural stem cells were isolated from adult human olfactory bulb — lines derived from these cells differentiate into neurons, astro- and oligoglial cells (Pagano S.F. et al., 2000).

Neural stem cells are found in the hippocampus of the mature rat brain (Brewer G.L., 1999; Gage F.H., 2000), mice (Kempermann G. et al., 1997 a, b), monkeys (Gould E. et al., 1999) and human (Kukekov V.G. et al., 1999; Svedsen C.N. et al., 1999). Shown that stem cells of hippocampus dentate fascia subgranular area give rise to progenitor cells migrating into the medial and lateral limbs of this structure, where they differentiate into mature grain-cells and glial elements. The axons of newly formed neurons in dentate gyrus can be traced to the field CA3, suggesting the involvement of these cells in a function of the hippocampus (Hastings N.B., Gould E., 1999). In the new cortex of adult monkeys formation of neurons migrating from the subventricular zone, found only in associative areas (Gould E. et al., 1999). In neocortical layer VI of mice, the de novo formation of pyramidal neurons was detected by 2–28 weeks after in-

jury and loss of native neurons of this layer (Magavi S.S. et al., 2000). In addition, about the postnatal neuronogenesis in the human brain evidences the data proving that during the period from 15 months to 6 years two-fold increase in the number of cortical neurons occurs (Shanke W.R. et al., 1998).

There are certain contradictions in the matter of primary localization of neural stem cells in the periventricular zone of the lateral ventricles. Confirmation of the fact that mature brain stem cells are localized in ependyma, serves the results of studies showing the possibility of isolating immature neural precursors from the central nervous system areas, which does not contain subependyme zones — the third and fourth ventricles of the forebrain, spinal canal of the thoracic and lumbar spinal cord (Laywell E.D. et al., 1999). With spinal cord injury increases the proliferation of central canal ependyma stem cells, which generate cells migrating and differentiating into astrocytes of glia-mesodermal scar (Johansson C.B. et al., 1999). Precursors of astro- and oligodendrocytes were found in the intact spinal cord of adult rats (Horner P.J. et al., 2000).

Established cross-plasticity of stem cells — after intravenous injection of hematopoietic cells expressing GFP to adult mice, micro- and astroglial cells were found in the neocortex, hippocampus, thalamus, brain stem and cerebellum (Eglitis M.A., Mezey E., 1997; Ono K. et al., 1999). At the same time, cloned stem cells of the brain introduced into the venous system of irradiated mice, formed in the spleen and bone marrow populations of myeloid, lymphoid and immature hematopoietic cells (Bjornson C.R.R. et al., 1999).

Regenerative medicine and diseases of the nervous system. In the field of neurology cell transplantation was the most effective in the treatment of Parkinson's and Huntington's diseases, Down syndrome, epilepsy, cerebral ischemia, stroke, cerebral palsy, injury of the brain and spinal cord. Methodical approach of substitution cells transplantation in neurosurgery provides a local introduction to the damage area of CNS undifferentiated neuronal stem cells or embryonic neural tissue as well as pre-differentiated into neurons embryonic or adult stem cells. According to one such tool, an injury of the CNS, as well as in hemorrhagic stroke from the damage zone is suctioned blood, and in its place with the help of the stereotaxic apparatus entered cells isolated from fetal brain (neural stem cells).

Efficiency of cell transplantation in the treatment of CNS lesions is determined by brain location behind of the barrier, which to some extent isolates the cell graft from the immune system of the recipient and obstructs the reaction of its rejection. Under such conditions, the low level of cell differentiation and the absence of major histocompatibility complex molecules on their surface significantly delayed the beginning of the immune response to transplanted cells. However, the glial inflammatory reaction to the genetically foriegn material is saved, which often leads to disruption of the hemato-encephalic barrier, infiltration of brain tissue by immunocompetent cells and the destruction of formed de novo neurons by immune mechanisms. Nevertheless, the duration of the recovery of the CNS functional defect is sufficient high and reaches after allogeneic neurons precursors transplantation from one year to three years (Snyder E.Y. et al., 1995; Rudenko V.A., 1998; Cameron H.A., McKay R.D.G., 1998; Otellin V.A., 1999; Bamber N.I. et al., 1999; Fukunaga A. et al., 1999; Tsymbalyuk V.I., 2000; Marciniak A. et al., 2000; Aleksandrova M.A. et al., 2001; Viktorov I.V., 2001; Sosunov A.A., Chelyshev Y.A., 2002; Sukhikh G.T., Malaytsev V.V., 2001).

Cell transplant rejection due to the fact that the differentiation of transplanted cells into neurons in loco morbi accompanied by expression on its cell surface markers of genetically foreign that triggers glial reaction and immune attack by the recipient organism. That is why nowadays intensively been conducted clinical trials on the use of autologous transplantation of hematopoietic and mesenchymal stem cells. Autologous hematopoietic and mesenchymal stem cells are usually obtained from the patient's ilium. Isolated cells differentiate in culture to the fibroblast-like and neuron-like cells, which are administered to patients: with traumatic brain injury — in the cavity formed after the extraction of hematoma, at stroke — endolumbal, at myelopathy — intravenously. Results of Parkinson's disease treatment by the method of stereotactic transplantation are characterized by an initial increase in symptoms, but three months after the surgery comes a significant clinical improvement. In recent years, for transplantation uses regional stem cells from the area of the olfactory epithelium.

Method of cell neurotransplantation is constantly being improved. Today developed criteria for evaluating its effectiveness with

glial fibrilary astrocytic protein (GFAP): if a patient's blood after transplantation increases the content of GFAP, neurotransplantation performed poorly, because this fact show that in the central nervous system formed not neurons but glial elements. The experiment proved the feasibility of using human neural stem cells to treat spinal cord injury. When dosed rats spinal cord compressional contusion after 6–7 days on the local of bleeding are formed cysts. With the help of dye bisbenzimidine shown, that neural stem cells migrate along glial and neural tracts and removes atrophy of the injured spinal cord. Investigation of traffic neuronal stem cells in the brain confirms their highest migration capacity, which opens up prospects not only for replacement therapy, but also for treating deep localized tumors of the CNS by the directed transport of IL-12 with neuronal stem cells as a vector (Chumasov E.I., 1990; Lendahl U. et al., 1990; Park K.I. et al., 1995; Davies S.J. et al., 1997; Otellin V.A., Petrova E.S., 1998; Petrova E.S. et al., 1999; Chekhonin V.P. et al., 1999; Temple S., Alvarez-Buylla A., 1999; Babiychuk G.O. et al., 2000).

Great contribution to the development of Ukrainian neurotransplantation has a team of specialists led by Professor V. Tsymbalyuk, whose works cover a wide range of problems of cell transplantation — from experimental research to clinical implementation of new original methods of treatment of severe lesions of the nervous system (Tsymbalyuk V.I., Pichkur L.D., 1996; Tsymbalyuk V.V. et al., 1998; 1999; 2000; 2001; 2002).

Stem space of the eye. The discovery of stem cells in the eye of mammals (Ahmad J. et al., 2000; Perron M., Harris W.A., 2000; Tropepe V. et al., 2000) led to a kind of research shock, which often happens in breaking long-entrenched views. In this case broke down the fundamental position about the inability of the eye, especially the retina, to regeneration. Until 2000, it was thought that mammal's ciliary folds contain only differentiated cells, which provide accommodation and secrete proteins into the vitreous (Link B.A., Nichi R., 1998). In the embryogenesis multipotent cells of retina germ are capable to differentiating into all types of retinocytes. Cells of the neuroepithelium initially divided symmetrically, which leads to the accumulation of cell mass necessary for the retina development. Then the division becomes asymmetric, resulting in one of the daughter cells retains multipotent, and the other differentiated. In the early stages of development are formed ganglion cells, cones, amacrinal and horizontal cells; late — rods, bipolar cells and Myuller glia (Chepko C.L., 1993; Harris W.A., 1997). In constantly growing amphibians and fish, as well as in chickens in the ciliary and the rim terminal areas of retina multipotent cells are preserved (Mitashov V.I., 1996; 2001; Wetts R., Fraser S.E., 1988), but in mammals only in the earliest stages of postnatal period in the terminal area of the retina are found proliferating cells, which are then not detected (Ahmad J. et al., 2000).

However, in experiment V. Tropepe et al. (2000) cells isolated from the ciliary folds of adult mice, proliferated in vitro, which was confirmed by proliferation marker BrdU. After 2 days the single cultured cells formed clones of pigmented cells, and after 5–7 days were formed spheroidal colonies containing both pigmented and depigmented cells, which could be subcultured up to 6 times. Moreover, the cells of iris, ciliary muscle and non-pigmented cells of ciliary folds spheroidal colonies did not form. In formed spheroids in the center of the colony were found large cells, which were attached to the substrate, whereas the peripheral cells expressed homeobox-containing genes Chx10 and neurofilaments. This transient population of small-differentiated cells contained precursors of shortly differentiating rods, bipolars and Myuller glia, which was proved by appropriate monoclonal antibodies. Similar results were obtained in experiments on rats (Ahmad J. et al., 2000): found that the conditions of culturing in the presence of FGF2 cells from the pigmented area of ciliary folds actively proliferating and, passing through a stage of nestin-producing transient population differentiated as rods, bipolar, ganglions and glial cells.

It is generally accepted that regional stem cells are undifferentiated multipotent cells producing several types of differentiated cells (Morrison S.J. et al., 1997; Temple S., Alvarez-Buylla A., 1999; Wei G. et al., 2000). However, mammals pigmented stem cells of the ciliary folds functions as the differentiated cells secreting proteins into the vitreous (Link B.A., Nichi R., 1998). They do not express nestin, but after depigmentation and dedifferentiation these cells were actively proliferating, express markers of neural-type differentiation and transform into neurons and glial cells. Such transformations of initially differentiated stem cells show their transdifferentiation, like the process that occurs with

the cells of the pigment epithelium in the adult newt retinal regeneration (Klein L.R. et al., 1990; Zhao S. et al., 1995; Sakaguchi D.S. et al., 1997).

The discovery of stem cells in the eye of adult mammals (mouse, rat, ox, human) is a sufficient basis for the revision of some established ideas about the differentiation and regenerative potencies of mammals eye tissues. Number of stem cells in pigmented ciliary folds is small (0,2 %), but quite enough for the manifestation of regenerative potentials. Currently mammalian pigmented cells of ciliary folds and peripheral region of lower vertebrates pigment epithelium, proposed to consider as homologous structures (Mitashov V.I., 2001). Preservation in these areas of proliferating elements with signs of stem cells that exhibit potency in transdifferentiation and subsequent formation of retinal cells, shows not only much broader regeneration potencies eyes of mammals, but also proves the reality of the existence of another mechanism for the formation of stem-spaces — transdifferentiation.

Regenerative medicine and eyes desiases. At the junction of neurosurgery and ophthalmology with use of allogenic cell transplantation achieved success in treating of few eyes diseases (pigmental degeneration of the retina, glaucomatous optic nerve dystrothia and other degenerative processes). Shown, that the introduction of neural stem cells in rabbit's subtenonic space in case of laser retinal lesions restores the retinal histological structure. Transplantation of embryonic neural tissue under the membrane of the n. opticus in rabbit methanol intoxication normalizes the ultrastructure of the optic nerve and significantly improves the functional state of the visual analyzer, which was proved by means of vison evoked potentials (Sergienko N.M. et al., 1998; Zhaboedov G.D. et al., 2000; Lutsenko H.S., 2000, Radchenko M.V., 2003).

Stem space of the pancreas. The uniqueness of pancreas is the coexistence of two different morpho-functional components — the cells of the exo- and the endocrine apparatus (Slack J.M.W., 1995). Nevertheless, recent embryogenetic studies have clearly shown that all types of pancreatic cells originate from single multipotent stem cells with the phenotype epithelial ducts (Kasper M. et al., 1991). A set of embryonic cytokeratins -4, -7, -8, -18 and -19, which is characteristic for all cells of a two-week human embryo, is revealed in the pancreas until 28 weeks of intrauterine development, and in the future remains unchanged throughout life only in the cells of ductal epithelium. Differentiation of pancreatic stem cells in the direction of acinar and endocrine lines is accompanied by loss of cytokeratins -4, -7 and -19. Mature acinar cells of the adult organism stably express cytokeratins -8 and -18, whereas their level is low in the differentiated endocrine cells (Schussler M.H. et al., 1992).

Stages of differentiation of endocrine cells from pluripotent progenitor cells have been well studied. The mechanism of morphogenesis of the islets of Langerhans involves a propogation of endocrine cells by gemmation (nesidioblastosis) from the epithelial lining of ducts, their accumulation between ducts and exocrine acini, followed by isolation. Such stem cells, or nesidioblasts, even in the pancreas of an adult organism can be induced to proliferation and differentiation into endocrine cells capable of producing a variety of peptide hormones (Bouwens L., De Blay E., 1996; Bouwens L., Kloppel G., 1996; Bouwens L. et al., 1997; Bouwens L., 1998 a, b). Unlike mature endocrine cells of adult animals capable of synthesizing only insulin, endocrine progenitor cells are multipotent and all hormone-specific genes are activated in them (Teitelman G., 1991; 1993). Similar islet cells simultaneously producing several hormones were also found in the human fetal pancreas (Bocian-Sobkovska J. et al., 1999). It has been established that polyharomonality is inherent to human and pig fetal pancreatic cells. They can synthesize and store different hormones, in particular insulin and glucagons (Lukinius A. et al., 1992), insulin and neuropeptide Y (Oberg K., 1996), and also gastrin (Chaundry A. et al., 1994; Gurevich L.E. et al., 2001), in the one and the same or different granules.

It has been proved that the highly differentiated endocrine cells (β-cells of Langerhans islets) does not represent the final, terminal stage of differentiation. On the contrary, the phenotype of islet cells remains ductile and under certain conditions genes responsible for expression of markers, which are characteristic of stem cells can be activated in them (Teitelman G., 1993). Among the markers of regional stem cells in the pancreas of adult animals, one should mention glucose transporter GLUT2, acidic β-galactosidase (Steiner D.F., James D.E., 1992; Wang T. et al., 1995), protonkogen bcl-2 (Bouwens L., De Blay E., 1996) and cytokeratin-19 (Bouwens L. et al., 1997). There are nestin-positive and hormone-negative cells at the periphery of

pancreatic islets of the adult organism, where usually the small positive group with respect to cytokeratin-19 cells are revealed, which do not form a duct structure (Hunziker E., Stein M., 2000). Moreover, pronounced ductility of exocrine acinar cells also suggests that they have properties of multipotent stem cells (Gurevich L.E. et al., 2001).

Regenerative medicine and pathology of endocrine system organs. The treatment of diabetes is the main trend of the regenerative medicine in endocrinology. Transplantation of stem cells after their in vitro differentiation in β-cells in the pancreas leads to reduction in blood sugar due to enhanced synthesis and incretion of the insulin. However, allogeneic islets of Langerhans lose their normal rhythm of insulin secretion, which poses a serious threat of hypoglycemic complications. There are reports that insulin producing cells can be obtained from mesenchymal stem cells of bone marrow, for this purpose conditioned medium from cells of embryonic pancreas is used (Repin V.S., Sukikh G.T., 1998; Verhuletsky I.E. et al., 2000; Kovalsk I.O., 2000, Repin V.S., 2001 a, b; Kot O.G. et al., 2002).

Ukraine has made considerable progress in the treatment of diseases of the thyroid, parathyroid, semens and other endocrinopathies by means of xenotransplantation of cells, organ cultures, or endocrine tissues (Bondarenko T.P. et al., 2000; Zubkova G.A. et al., 2000; Lutsenko N.S. et al., 2000; Sichinava P.M., 2000; Genik S.M. et al., 2002). Professor I.S. Turchin has made great contribution in the development of xenotransplantation trend in the regenerative medicine (Turchin I.S. et al., 2000–2003).

Stem space of the liver. Stem Space of the Liver has a unique replicative potential as it consists of three components at once: hepatocytes, which exhibit properties of unipotent polyploid cells, oval cells of the bile duct and bone marrow stem cells. Hepatocytes in mammals are differentiated polyploid cells, which under normal conditions are stably located in the phase G0/G1 of cell cycle. The duration of such mitotically inert hepatocytes corresponds to human lifespan (Uryvaeva I.V., 2001). However, in case of partial loss of liver parenchyma hepatocytes exhibit almost limitless ability to multiply at an extremely high rate of regeneration — in course of multiple surgical resection from 70 to 80 % of cell mass of the liver parenchyma, its restoration occurs within 5–6 days. Experiments with intoxication by carbon tetrachloride have shown that complete renewal of diseased liver tissue occured even by eightfold introduction of CCl4 with an interval of 1 month (Factor V.M., Uryvaeva I.V., 1980). It has been proved in the transgenic mice (ALuPA, Fah-/-) that mature hepatocytes, as compared to other somatic cells, have a higher Hayflick limit, which shows the capability towards more than 100 replicative cycles and fully repopulate liver in animals of 6–8th transplant generations (Sandgren E.P. et al., 1991). Consequently, hepatocytes are characterized by their capability of self-maintenance throughout the life of an organism, which is one of the main characteristics of the cells in stem-spaces, and hence one may consider differentiated parenchymal liver cells as unipotent stem cells (Thorgeirsson S. S., 1996; Fausto N., 1997; Laconi E., 2000). Unipotency of hepatocytes is associated with polyploid set of chromosomes. Propagation of hepatocytes is characterized by alternation of acetokinetic and completed mitosis in the postnatal ontogenesis, which correspondingly leads to a uni- and binuclear state. Binuclear diploid cells are not capable of self-reproduction, as a result of which single diploid liver cells of adult animal are stored as precursors of a number of polyploid hepatocytes. After liver damage mitosis without cytokinesis is excluded and cell division occurs according to conventional, completed type, as a result of which a proliferating population of hepatocytes become uninuclear. Thus, binuclear cells are laid in course of the normal slow growth of the liver as potential sources of future clone of mononuclear polyploid hepatocytes with unlimited number of offspring under the conditions of regeneration (Uryvaeva I.V., 2001).

Oval cells localized in the terminal bile duct — Goering tubules is one more stem space of liver. It is believed that the oval cell is a partially committed phenotypically recognizable cells originating from the brainstem of the latent stock of the liver (Alison M.R., 1998; Factor V.M. et al., 1994). The cells of this stock constitute so-called optional liver stem stock since oval-cell proliferation starts only when the division of polyploid hepatocytes is blocked, which is convincingly demonstrated in experiments with dipin and retrorsin (Uryvaeva I.V. et al., 1996; Gordon G.L. et al., 2000).

Stem-spaces are not necessarily localized in the organ, in which loss of cell mass is replenished by them. Extrahepatic sources of stem cells are also established for liver, which are capable of transformation into oval cells

and differentiated hepatocyte line. After lethal irradiation of animal, bone marrow transplants from male to female rats led to chimerization of liver with formation of hepatocytes, oval cells and bile duct epithelium containing Y-chromosome (Petersen B.E. et al., 1999). Similar results were obtained in course of heterosxual bone marrow transplantation using intravital biopsy or after removal of the liver due to a pathological process (Alison M.R. et al., 2000). Acinar pancreatic tissue is one more extrahepatic stem space for the liver, which develops from the embryonic germ common with the liver (Rao S. et al., 1989).

Regenerative medicine and liver diseases. Despite extremely high regenerative capacity of hepatocytes, there are quite a number of diseases, in which the hepatic failure is developed. Moreover, these diseases can be either acute (toxic or viral hepatitis), and chronic (autoimmune active hepatitis) and the number of cases requiring liver transplantation in terminal stages of liver disease increases progressively. The current method of liver transplantation is very effective, but extremely difficult in technical terms and requires considerable resources. In addition, problem of donor liver tissue remains unsolved. An alternative to a liver transplant operation is transplantation of hepatocytes, which has three possible versions: autotransplantation of hepatocytes generated in vitro from autologous stem (hematopoietic or mesenchymal) cells of the patient, allotransplantation of donor's hepatocytes and allotransplantation of hepatocytes of donor's stem cells. In the latter two cases, the need for immunosuppressive therapy programs remains, but much more simple, which use smuch smaller doses and the number of immunosuppressive agents than in liver transplantation. Another direction of the regenerative medicine in hepatology involves the use of unipotent stem properties of hepatocytes by using no cells and fetal liver extract, which stimulates the division of patient's own hepatocytes. The effectiveness of this method are morphologically and biochemically proven in experimental liver cirrhosis (Repin V.S., Sukhikh G.T., 1998; Petrenko O.Yu. et al., 2000; Subota N.P. et al., 2000; Tutchenko M.I. et al., 2000; Batanov A.N. et al., 2002; Kotenko O.G., 2002; Sukhikh G.T., Shtil A.A., 2002).

Mesenchymal stem space. Mesenchymal stem cells first appear in the neural in the embryogenesis crest, from where they migrate creating a primary framework for future provisory bodies, being as if their skeleton of a three-dimensional spatial orientation. In addition, progenitor stromal elements control the development of embryonic parenchymal organs due to synthesis of a strictly defined combinatorial growth factors(TGFα, KGF, HGF, EGF) and are source of cells of connective, bone, cartilage, fat and muscle tissue in postnatal development, they generate background signals to maintain the viability and proliferation of progenitor cells (LIF, SCF, M-CSF, Flt-3, IL-6, IL-7, IL-8, IL-11, IL-12, IL-14, IL-15), form the tendons and the stroma that supports hematopoiesis (Repin V.S., 2001; Bianco P. et al., 2001).

On prolonged administration into the bloodstream mesenchymal stem cells are implanted into different organs of animals-recipients and differentiated into the blood cells, myocytes, cardiomyocytes, adipocytes, tendotsity, cartilage and bone cells as well as into the fibroblasts. Their introduction into the ventricles of the brain is accompanied by migration of mesenchymal stem cells into the parenchyma tissue of the CNS with the formation of glial cells and neurons. In addition, mesenchymal stem cells are capable of conversion into hematopoietic stem cells (Robertson E., 1986). The main mesenchymal stem space in the adult body is bone marrow tissue, where a network of immature stromal cells is located in the recess between the sinusoids and bone. Mesenchymal stem cells are dormant, do not express receptors for the adhesion molecules (CD34, VCAM, ICAM, CD44, CD29, receptors for collagen I and III type) and does not attach to the feeder layer. Even progenitor stromal cells exhibit adhesiveness, which are multiplied in the culture while maintaining low cell differentiation markers (SH2, SH3, CD106, CD54, CD44, CD71, CD90, CD106, CD120a, CD124) when there are no antigens of hematopoietic stem lines (CD34, CD14, CD45). When added into the culture medium for inductor of the synthesis of cAMP, inhibitors of phospholipases and thromboxansynthase virtually all immature stromal cells form adipocytes. From the same pool of progenitor under the influence of TGFα chondrocytes are formed in serum-free medium, while bone cells can be obtained in culture with fetal serum adding to the background of blockade of phospholipase donator of inorganic phosphate and ascorbic acid (Shamblott M.J., Gaerhart J., 1998).

According to our opinion, the most important is the detection of the circulating pool of mesenchymal progenitor cells: immature

CD34-negative cells were found in blood of adult mammals. These cells are attached to the substrate in culture and form colonies of fibroblast-like cells, demonstrating the ability to differentiate into adipocytes, myofibroblasts, bone marrow stroma tissue, chondrocytes and osteocytes. A small portion of CD34 — cells from the bloodstream returns back into the bone marrow, where it is transformed into a line of CD34-positive hematopoietic cells. Thus, the recycling of progenitor mesenchymal cells in the blood stream ensures the stem balance of tissue regions of the body through a common cell pool of bone marrow (Hanss R. et al., 2000). In other words, the bone marrow is a self-renewing multipotent stem space of non-specific mesenchymal stem cells providing the derivatives of mesenchymal cells to the body throughout life.

Specific stromal regenerative capacity is reserved directly in the tissues. Stellate cells are found in the primary culture of cells isolated from human skeletal muscle, which grow in culture without signs of differentiation, but by adding dexamethasone they start to differentiate to form cells of skeletal and smooth muscle, bone, cartilage and adipose tissue. Population of stellate cell precursors is derived from non-specified mesenchymal progenitor cells of bone marrow and is characterized by myogenic satellite cells (Bianco P., Robey P., 2000). Cells expressing STRO-1 — a marker of stromal cell precursors, but not having a marker of osteoblast — alkaline phosphatase have been revealed in primary cultures of human bone tissue revealed. These cells have the phenotype of proosteoblast with low capability of the forming the mineralized bone matrix without expression of osteopontin and the receptor of parathyroid hormone. Transient cells from intermediate to fully differentiated osteoblasts have also been detected, which originate from STRO-1-positive cells not expressing alkaline phosphatase (Deans R.J., Moseley A.B., 2000).

The least differentiated precursors of adipocytes in adipose tissue are stromal-vascular cells. These cells, along with mesenchymal progenitor cells of bone marrow origin, can differentiate into adipocytes under the influence of glucocorticoids, insulin-like growth factor-1 and insulin. In addition, the stromal-vascular cells form chondrocytes, while there are are cells in the adipose tissues of bone marrow capable of differentiating into adipocytes as well as into osteoblasts (Pittenger M.F. et al., 1999).

Most of the vessels formed from the endothelial tubes, which envelops vascular smooth muscle pericytes originating from undifferentiated perivascular mesenchymal progenitor cells. This group of immature stromal muscle expresses α-actin of soft muscles and the receptor for platelet-derived growth factor (Sukhikh G.T. et al., 2002). Hence, along with distant migration of vascular bed, carried short distance or local movement of mesenchymal progenitor cells within the tissue during repair of cartilage, muscle regeneration and other regenerative processes are also accomplished. Impression is created that CD34-negative cells circulating in the blood perform the tasks of the linear brigade of emergency aid, while regional immature stromal elements localized in tissues ensure «urgent repair» of body «at the sites». Replenishment of tissue progenitor stromal mesenchymal reserve is ensured by mesenchymal space of the bone marrow.

Regenerative medicine, and pathology of bones and joints. Mesenchymal stem cells are primarily used in the traumatology. Reconstruction of the bones, ligaments and cartilage usually (90 %) does not require immunnosupression since the recovery of skeletal elements of the ligamentous apparatus or synovial-cartilage complex is performed using the patient's own cells. For a long time it was considered that restoration of hyaline cartilage is impossible even when cellular technology is used, however in 2003 conditions were found for the differentiation of mesenchymal stem cells in bone marrow in the hyaline cartilage and the first successful reconstructive surgery has been performed on the joints, positive results ahave been clearly confirmed by arthroscopy. There was striking success of cell transplantation surgery for the restoration of bone defects by using a matrix of cellular reconstruction, which also has a number of methodical techniques. In case of bone defects of craniofacial area porous plastic matrixes are used, which have exactly the same shape and size of the lost bone area. «Seeding» of the patient's own mesenchymal stem cells is performed on such matrix p, which under the influence of a certain range of growth factors and cytokines form bone tissue. Defect of jaw is replaced with a porous carrier of mesenchymal stem cells in bone marrow of the patient in the Clinic of Plastic Reconstructive Medicine, which is completed by osteofication of peculiar «graft». In case of complex fractures of long bones cadaveric bone is used to replace

the defects, from which organic material is burned in a muffle furnace or, conversely, removeal of the mineral matrix by treatment with acids is accomplished. Mesenchymal stem cells are implanted on the remainder of the skeleton (mineral or organic), said cells are directionally differentiated into cellular elements of bone tissue and its connective tissue matrix. In both cases, the rejection of such implants-transplants did not occur. Osteogenic potential of mesenchymal stem cells is originally determined to the sufficient extent. From a single mesenchymal bone marrow cells colonies of cells are grown and subjected to incubation in vivo in the diffusion chamber, i. e. without direct cell contact. It is established that 3 kg of bone tissue is formed from 500 mg of these cells and overall life of the osteogenic potential of mesenchymal stem cell pool reserved in the bone marrow is thousand times greater than the real needs of the human body, even if there is hypothetical daily fractures (Alan F., 1994; Astakhov V.S. et al., 2000; Gaiko G.V. et al., 2001; Manuilova E.S. et al., 2001; Chailakhyan R.K. et al., 2001; Bianco P. et al., 2001).

Stem space of the skin. It is well known that the renewal of the epidermis is occured at the expense of stem cell space capable of self-renewal and differentiation (Morrison S.J. et al., 1997). Epidermal stem cells were identified by the peculiarities of accumulation of ^{3}H-thymidine as a cell without exciting the radioactive label after a single dose (Potten C.S., 1983), or, conversely, as the cells with long-lasting activity after prolonged administration of labeled thymidine (Bickenbach J.R., 1981). The growth of human keratinocytes in culture is characterized by the formation of holoclones, meroclones and paraclones. Holoclones consist of small rounded basal stem cells and exhibit a maximum proliferative capacity producing from 1500 to 4000 daughter cells per day. Holoclone cells in culture can withstand up to 100 passages. Meroclones contain transient keratinocytes with different proliferation capacities. Paraclone cells are characterized by low proliferation potential (up to 15 divisions) and exposed to the terminal differentiation (Barrandon Y., Green H., 1987). Three in vivo (not histologically, but in terms of the kinetics of cell populations) zones are also singled out. Cells of the basal layer proliferate at very low speeds they are almost in a state of rest. Actively dividing along short-cycle transient cells was located above them, which, in turn, are the source of the third, differentiated layers of mature keratinocytes. By this organization of cell growth formation of a large number of differentiated cells occur due to a small number of cell divisions of stem space (Watt F.M., 1998), which ensure the growth layers of keratinocytes in culture in course of autotransplantaion of skin (Terskikh V.V., Vasiliev A.V., 1999).

Absolute marker of epidermal stem cells has not yet been found, however it has been shown that keratinocytes are capable of forming colonies characterized by the high level of expression of integrins $\alpha_2\beta_1$, $\alpha_3\beta_1$ and $\alpha_5\beta_1$ (Jones P.H., Watt F.M., 1993), while cell cultures expressing integrin β_1 after transplantation completely restores the epidermis (Jones P.H. et al., 1995). Moreover, it has been shown by means of double-marker $\alpha6^{bri}10G^{dim}$ that epidermal stem cells possessing the highest ability of regeneration constitute about 10 % of immature cells in the epidermis of skin (Li A. et al., 1998), whereas one may use up-regulation of expression of PA-FABP — protein, which binds fatty acid of epidermis, as a marker of transient cells (O'Shaughnessy R.F. et al., 2000).

Functionally, the epidermis consists of epidermal proliferative units, which have a central cluster that contains stem cells and Langerhans cells, as well as proliferating cells located above the cluster in the form of monetary column (Potten C.S., 1974; 1983). Stem cells of the basal layer of the epidermis or hair follicles at a low density of seeding on feeder layer of irradiated cells also form clusters in the culture and the number of cell «grains» on them corresponds to the number of divisions being passed (Morris R.J., Potten C.S., 1994).

Epidermal stem cells localized at the basal membrane, as well as undifferentiated cells of the outer sheath of human hair follicles are the main stem space of skin (Cotsarelis G. et al., 1990; Yang J.S. et al., 1993; Rochat A. et al., 1994). Another contender for the area of stem cell space is the sweat glands (Miller S.J. et al., 1998), however on recuticularization of wound surface cells of sweat glands, unlike migrating stem cells of hair follicles (Limat A. et al., 1991; Taylor G. et al., 2000), never form the epithelium of the skin identical to natural one (Terskikh V.V., Vasilieva A.V., 2001).

Regenerative medicine and skin blemishes. As in trauma, in the transplantation of skin preference is given to the patient's own stem cells, which eliminates the problem of transplant rejection. In recent years, quite

effective cultivation technology and skin grafts based on the implementation of the pluripotent potential of mesenchymal stem cells in bone marrow patient has been developed. Resulting in vitro fibroblasts are fixed on the absorbable biopolymer matrices, and then, under the influence of the natural microenvironment in the affected area or skin defect are subject to differentiation into keratinocytes. Method for separating stem cells from the basal layer of human skin is also effective. Seperated cells are grown to the stage of transformation in fibroblasts. Microcarrier of fibroblasts is collagen, which forms a layer of dermal keratinocytes. The principle of the method is based on destratification (induction of death of all cells except the stem cells — the basal ones and localized in the hair follicle and in sebaceous glands) by means of the cultivation of the skin in a medium without calcium and mitogens for three weeks. After transplantation of cells on complete incubation medium, cells multiply within three days and subsequent transfer to fresh medium with growth factors after one week leads to the formation of keratinocytes, which can be transplanted to patients with burns. The resulting dermal equivalent obtained in this manner (a layer of fibroblasts in fibrin gel) and the live skin equivalent consisting of a layer of keratinocytes, biodegradable mesh and a layer of fibroblasts are successfully used in the treatment of superficial and deep skin burns (Viktorov I.V., 2001; Lucas L.L., Vasilovskaya S.V., 2001; Manuilova E.S. et al., 2001; Terskikh V.V., Vasilieva A.V., 2001; Malaytcev V.V. et al. 2002; Sukhikh T. et al., 2002).

Regenerative medicine and heart — blood vessels diseases. Cell transplantation in cardiology began his journey, as in other fields of medicine, with experimental studies. It has been proved in one of the first reports on the possibility of differentiation of ESCs into cardiomyocytes in the experimental myocardial infarction that ESCs of donor labeled with green fluorescent protein is embedded into the zone of ischemic damage of the heart muscle, where they are subjected to the differentiation into cardiomyocytes and replace non- crotized heart tissue. This effect has been repeatedly replicated in other laboratories around the world and has already found clinical application in different versions: the administration of ESCs, autologous or allogeneic stem cells, previously differentiated in vitro into cardiac myoblasts directly into the zone of necrosis of the heart intravenously or through a catheter into the coronary arteries. It is clear that the first and third options require the implementation of the protocols of immunosuppression. The first clinical trials of treatment of coronary atherosclerosis in humans with allogeneic hematopoietic stem cells have been initiated: laters are administered directly into the coronary arteries, which contributes to activation of vasculogenesis with the formation of new blood vessels that ensures a «shunt» blood flow to ischemic myocardium. The methods for generating a self-developing capillary network are being developed: endothelial cells are grown in cell cultures of ESCs and then the resulting in vitro endothelial cells are transferred to the porous surface of microtubules, which are perfused by feed medium. Autologous capillary network generated in this manner can be used in ischemic lesions of internal organs without the use of immunosuppressive drugs. Patient's own mesenchymal stem cells are differentiated in vitro into cardiomyocytes for the treatment of myocardial infarction in human being, which are then administered into the coronary arteries or the border zone of necrosis in cardiac muscle. The effect of the positive dynamics of heart perfusion and regional cinematics in such a therapy has been proved by the projection of radiographs of heart obtained with ^{201}Tl-labeled cells in the radiographs obtained by tetrafosmin Tc-90m, which «highlights» the entire myocardium. Method is approved, according to which monocyte fraction of bone marrow cells of the patient is administered through a catheter directly into the heart with pinching sections of coronary artery by aerosol blown with air. In order to prevent retransplantational arrhythmias, cell suspension was administered fractionally, 4–5 times, but when there is single catheterization. It is reported that the administration of G-KSF (Neupogen) mobilizes own stem cells in the bone pulp of patient that facilitates the neovascularization of the heart and restore the damaged cardiomyocytes. Embryonic myoblasts are used in the pathology of vascular and heart diseases. Effective and positive remodeling of the heart has been proved in severe defects in children — branching of left coronary artery from the left pulmonary artery. It is assumed that the effect of cell transplantation is based on angiostimulating effect since the results obtained in treatment of patients with vascular pathology are consistent using such angiostimuline. It is shown, that the selection of

valves from pig heart, their devitalization followed by seeding endothelial or smooth muscle cells derived from autologous hematopoietic stem cells in bone marrow prevents calcification of transplanted valves and greatly reduces the intensity of the reaction of graft rejection. In the experiment, a single intravenous injection of moderate doses of embryonic pluripotent progenitor cells normalizes systemic arterial pressure in spontaneously hypertensive rats for 1 month (Henon P.R., 1993; Gage F.H., 1998; Gearhart J., 1998; Lukash L.L., Vasilovskaya S.V., 2001; Manuilova E.S. et al., 2001; Repin V.S., 2001 a, b; Malaytcev V.V. et al. 2002; Kukharchuk O.L. et al., 2003).

Stem space of the muscle tissue. Human skeletal muscle consisting of a multinuclear syncytium contains mononuclear cells capable of proliferation when cultured in vitro (Holdfeid R., Engl A.G., 1994) and known as satellite cells (Allbrook D., 1981; Law P.K., 1994). Among the features, according to which satellite cells can be included in stem space of muscle tissue, one should note their presence in all skeletal muscles, as well as fetal clonality satellite cells, which buds from the somites and mature independently of them showing a distinct heterogeneity virtually without fuzogenic activity in mature muscle tissue. Formation of satellite cells in embryogenesis and in postnatal ontogenesis is associated with thin non-innervated myofibrils. It is in the process of atrophy of fibers, which did not receive innervation, satellite cells are formed (Repin V.S., Sukhikh G.T., 1998).

Normally, satellite cells are dormant, but when muscle tissue is damaged they are activated and enter into the cell division cycle. Dividing descendants of satellite cells form new muscle fibers, while in culture they are multiplied to form myoblasts (Walsh F.S., Ritter M.A., 1984; Anderson J.E., 2000). In the process of culturing myoblasts of the spectrum there is a change in gene expression and proteins specific to muscle tissue appear, which is completed by myoblast fusion in multinucleated miotubes (Walsh F.S., Ritter M.A., 1984; Holdfeid R., Engl A.G., 1994). In this case, regeneration of skeletal muscle resembles embryonic myogenesis: satellite cells are divided into two pools — one of them is immortal immature population, while the other enters into an irreversible path of differentiation by c-transcriptase MyoD and other gene products ensuring myogenesis (myogenin, myf-5, myf-6) (Rantanen J. et al., 1995). Many satellite cells actively express the gene MyoD in the human regenerating muscle. However, the number of MyoD-positive satellite cells declines sharply with age, which is correlated with the disappearance of the regenerative capacity of muscle in elderly people (Repin V.S., Sukhikh G.T., 1998).

The ability of myoblasts to form syncytia is coupled with their unique ability to integrate pre-existing myofibrils, which allows rectification of genome damage of skeletal muscle. It is shown that myoblasts are capable of delivering healthy donor gene that restores the synthesis of dystrophin into the muscle tissue of patients with Duchenne myodistrophy (Mendell J.R. et al., 1995; Svensson E.C. et al., 1996; Shishkin S.S. et al. 1999), while in case large-scale transplants positive therapeutic effect is accompanied by expression of the dystrophin gene for several years (Terekhov S.M. et al., 2001; Law P.K. et al., 1997).

Immunology of cells transplantation. Considered in the first two parts of the review a large group of regenerative medicine methods refers to the replacement cell transplantation and is based on the principle of embryonic stem cells preliminary multiplication in culture and their subsequent differentiation into specialized cells of the affected organ. The main problem that arose in the development of this regenerative medicine area, involves in the separation of pure ESCs-lines. Partialy it is allowed by defined set of ESCs markers, which consists of Oct-4, SSEA-1, SSEA-3, SSEA-4, DAPI, TRA1-60 and embryonic alkaline phosphatase. To identify the cells of early hematopoiesis monoclonal antibodies against CD133 (AC133) are being used. Besides, was developed magnetic column which allows isolating clean fraction of bone marrow early hematopoietic cells ($CD34^-$) without performing additional analysis (Gage F.H., 1998; Gryshchenko V.I. et al., 2000; Domaratskaya E.I. et al., 2001; Lukash L.L., Vasilovskaya S.V., 2001, Novik A.A., Bogdanov A.N., 2001, Repin V.S., 2001 b).

Principally different direction of the regenerative medicine based on the use of large doses of embryonic/fetal progenitor cells (E/FPC) and realizes by the effect of the adult organism's system control antigenic homeostasis reinstallation (the effect of Kukharchuk-Radchenko-Sirman) (Kukharchuk O.L. et al., 2002) that solves one of the most important issues of cell transplantation — the problem of allogenic cell material rejection

(Bakay R.A. et al., 1998; Ivory O.G., Seleverstov O.V., 2000; Slyusarev O.A. et al., 2002; Askenasy N., Farkas D.L., 2002). Prolonged chimerism of blood cells after hemotransfusion, as well as great therapeutic efficacy of high doses of stem cells (Zotikov E.A., 2001; Shevchenko Y.L., Zhiburt E.B., 2002; Askenasy N. et al., 2002; Fandrich F. et al., 2002; Down J.D., White-Scharf M.E., 2003) evidences an active interaction of transplantable cells with hematopoietic and immune systems of the recipient, whose essence conludes in induction of immunological tolerance.

The mechanism of immune system replacement involves creating a new database of immunocompetent cells and the simultaneous reprogramming of the major histocompatibility complex (MHC) control system. After introducing high doses of E/FPC the latter settles in the thymus and bone marrow tissues. In the thymus E/FPC are differentiate into dendritic, interdigital and other epithelial-stromal cells elements. In the process of E/FPC differentiation in the thymus, along with its own MHC-molecules are expressed MHC-molecules which are geneticaly determined into donor cells, i. e., establishing a double standard of MHC-molecules, by which realises the positive and negative selection of T-lymphocytes. In the bone marrow differentiation of E/FPC occurs (respectively to microenvironment) in the direction of hematopoietic progenitor cells and stromal cells elements. Replacement of the recipient immune cells in the process of system control antigenic homeostasis reinstallation carried out not discretely, but through a phase of immune chimerism with the gradual destruction of mature lymphocytes, stem and progenitor cells of the host organism by apoptosis mechanisms. Thus, the update of the recipient control antigenic homeostasis effector link occurs by the well-known mechanisms of positive and negative selection formed de novo T-lymphocytes via a double standard MHC-molecules of the recipient and donor E/FPC (Kukharchuk O.L. et al., 2002).

Is it principally possible of existance in nature the double standard of main histocompatibility complex molecules, by which effectively carried out positive and negative seletion of T-lymphocytes? Answer to this question is immune system of truly hermaphrodites — in thier embryogenesis no crossingover and no division of parents genome. As a result, tetraploid truly hermaphrodites do not rejects transplanted organs of parents, both mother's and father's organs. This fact convincingly proved in experiments on tetraploid mices (Royt A. et al., 2000; Kukharchuk O.L., Radchenko V.V., Sirman V.M., 2002).

Reprogramming of the immune system by using high doses of E/FPC not only allows to perform the cells transplantation without subsequent prolonged use of immunosuppressive drugs, but also opens up entirely new perspectives in the treatment of autoimmune diseases.

According to modern concepts, the specificity of T- and B-lymphocytes receptors formed coincidently, which naturally leads to the appearance of cells with a receptor field capable to react with antigens of own body, that is, constanly creating pool of autoreactive lymphocytes, for which counteracts the autologous tolerance mechanisms. Natural immunological tolerance both central and peripheral is not created in embryogenesis and is not encoded genetically, as previously assumed, but is constantly formed in ontogenesis. That is why the number of autoimmune diseases in which antibodies produced to the body's own modified by pathological process antigens seems to be entirely very low, whereas on forefront plan in the pathogenesis of autoimmune aggression moved antibodies, appearing due to the breach in the system of tolerance induction to own antigens of the organism, which in this case «skips» autoreactive T-lymphocytes through a thymic negative selection checkpoint. Subsequent launch of autoimmune aggression mechanisms is often triggered by microbial antigenic mimicry or adjuvant impact. In other words, an autoimmune disease in their predominant majority are not the result of acquired changes in the antigenic composition of an organism, but are the result of disturbances in the immune system, which should control and protect this antigenic composition (Royt A. et al., 2000).

Thus, replacement of damaged immune system to the new (reprogramming of the body antigenic homeostasis control system) in autoimmune pathology is pathogenetically approved, however does not removes the consequences, but the cause of disease i.e. cell transplantation aiming to substitute the damaged immune system in autoimmune diseases have an effect of pathogenetical treatment alternatives that do not currently exist.

Aging and stem-spaces. It is well known that autoimmune pathology, along with arterial hypertension and atherosclerosis (senile triad), is the prerogative of the aging organ-

ism. According to one of theories considered, that the basis for the development of senile triad is the age, so-called accidental involution of the thymus which leads to a weakening of the positive and negative selection of T-lymphocytes mechanisms with subsequent activation of autoaggressive clones of immunocompetent cells. In this regard, particular attention draws message evidencing about the effect of rejuvenation (by the external symptoms) and acceleration of the reproductive function after experimental or clinical use of stem cells (Kurtzman J., Gordon Ph., 1976).

Analysis of existing theories of aging shows that one of the key gerontology issues is the question about the indentity of the cell and multicellular organisms aging mechanisms (Frolkis V.V., 1991; 1998; Frolkis V.V., Muradian H.K., 1992; Repin V.S., 2001 a).

By studying the biology of stem cells we found a grip for the development of new ideas about the aging process, considering itself from the viewpoint to body stem-spaces depletion theory.

Beneath the stem-spaces, we understand the pool of regional (adult) stem cells (mesenchymal, neural, hematopoietic stem cells, the basal stem cells of the skin, intestine, endocrine epithelium, ciliary folds pigment cells, etc.), called to compensate cells loss in specific tissues in the process of remodeling organism.

Remodeling of the body — this is a uninterrupted renewal of cells composition of all tissues and organs due to cells of stem-spaces throughout the whole life of mammals multicellular organism, in which all differentiated cells have limited term of life.

It is known, that in different organs and tissues the death and renewal of cells occur at different speed. Therfore physiological regeneration is realized in two ways. In the first option duplication of differentiated cells with the formation of identical genotypes and phenotypes descendants occurs. The second way involves in the replacement of dying cells by differentiated descendants of early undifferentiated precursors. In this case neocytogenesis occurs due to multipotent stem cells capable of self-renewal and the formation of committed progenitor cells that undergo final differentiation under the influence of the tissue microenvironment (growth factors and cytokines).

In our opinion, particular regional multipotent stem cells create the stem-spaces of an adult organism, which is the morphological equivalent of the body stabilizing vitality and prolong life expectancy process.

Thus, to understand the mechanisms of aging, we offer a theory of the body stem-spaces depletion, the main positions of which are as follows:

1. Aging is a permanent reduction in the size of the body stem-spaces.

2. The number of cells in stem-spaces is determined that defines the level of proliferative capacity of each stem-spaces.

3. The dimensions of stem-spaces determine the rate of aging of the separate organs, tissues and body systems.

4. After depletion of cells reserves in the stem-spaces, the intensity and rate of multicellular organism aging is determined by the mechanisms of aging somatic differentiated cells within the Hayflick limit.

5. At the stage of postnatal ontogenesis expansion of the body's stem-spaces for increase the longevity and quality of the individual life is possible through introduction of allogenic embryonic progenitor cells, which is achieved only in case of simultaneous reprogramming the immune system of the recipient.

According to the main position of this theory, aging is a permanent reduction in the size of the body stem-spaces. Under the stem-spaces, we understand the regional (adult) stem cells pool (mesenchymal, neural, hematopoietic stem cells, progenitor cells of the skin, gastrointestinal tract, endocrine epithelium, pigment cells of ciliary folds, etc.), which is replenished by cell loss of corresponding tissue during the remodeling of the organism. Remodeling of the body — this is renewal of cells composition of all tissues and organs by cells of the stem-spaces, which has uninterrupted characteristics and continues throughout the all life of a multicellular organism. The number of cells in stem-spaces are determined that defines the limited size (the proliferative potential) of each stem area. The dimensions of stem-spaces determine the rate of aging of individual organs, tissues and body systems: lesser the dimension of the stem-spaces the faster aging of the organ takes place. After depletion of cells stem-spaces reserves the intensity and the rate of a multicellular organism aging are determined by the mechanisms of somatic differentiated cells aging within the limit Hayflick: mature cells are capable to divide only 40–60 times.

Thus, during postnatal ontogeny the expansion of stem-spaces can increase the duration and quality of life, as such therefore stem cells reserves are renewing and remodeling of aging organism realizes due to allogenic stem

cells. The expansion of stem-spaces can be achieved by introduction of high doses of allogenic embryonic progenitor cells under the condition of simultaneous reprogramming the recipient immune system as such without these introduced cells will be rejected.

It should be noted that the main positions of our proposed stem-spaces theory can significantly change the existing notions not only about the mechanisms of aging, but also about the disease, as well as the consequences of its modern treatment. We give merely some examples.

• According to the theory of stem-spaces depletion, the diseases can develop (appear) as a result of pathology into the cells of stem-spaces (tumors, hypo- and aplastic anemia, immunodeficiencies, etc.).

• Depletion of mesenchymal cells stem space disrupts the remodeling of the connective tissues that leads to the appearance of external signs of aging.

• Depletion of endothelial stem cells reserve causes the development of hypertension and atherosclerosis.

• Small sizes of the thymus stem space determine its progressive age involution.

• Premature aging is a consequence of small sizes of the all body stem-spaces.

• Drug and non-pharmacological stimulation of stem cells reserve improves quality of life by reducing its duration, as it decreases the sizes of the stem-spaces.

• Low efficiency of modern geroprotectors is due to their protective effects on aging differentiated somatic cells rather, than body stem-spaces.

• Stem-spaces of long-lived people exceeds above the average population size.

• A protective action on aging cells, incorporating into the Hayflick limit, leads to a prolongation of senility, but does not improve quality of life.

• Positive effects of acupuncture, homeopathy, monochromatic laser light, ultraviolet blood irradiation, electromagnetic radiation, hypoxic training, and low doses of ionizing radiation (hormesis effect) are associated with cells of stem-spaces mobilization, which also reduces life duration.

It is known that during the period of the body maturity and its aging normological relay and the natural death of cells is realized via apoptosis. At the same time, the size of cells populations' capable to uninterrupted renewal is mainly determined by factors that prevent apoptosis. In other words, apoptosis plays an important stabilizing role in maintaining the optimal number of cells in a multicellular organism. Apoptosis, unlike necrosis, does not cause formation of leukocyte infiltrates and does not elicit the growth of connective tissue with result of sclerosis or fibrosogenesis. Outcome of apoptosis, as regulated cell death is cells regeneration (Lushnikov E.F., Abrosimov A.Y., 2001). It is logical to assume that the same factors that trigger apoptosis simultaneously are inducers of proliferation and differentiation of stem-spaces cells.

It should be noted that practically all stem cell research of adult mammals confirm the concept of Schofield (Schofield R., 1978) about the importance of the cell microenvironment or «niche» — a combination of growth factors and molecules of the extracellular matrix which provide the conditions necessary to maintain the phenotype of stem cells, and in the absence of these descendants of stem cells turn into differentiation or undergo apoptosis (Rodeck U. et al., 1997; Terskikh V.V., Vasiliev A.V., 2001).

Maintaining the size of stem-spaces depends on the cells autonomous regulators modulated by external signals. In the role of such regulators are the factors of asymmetric cell division and genes expression control that determine the stage of committing and the number of mitoses. External signals that influence on the further fate of stem cells provides their microenvironment.

Thus, within the «stem-niche» carried out information exchange between non-committed and committed precursors, as well as between them and the surrounding cells. Proposed, that inducers of differentiation along with mesenchymal and non-mesenchymal cells and their products (growth factors and extracellular matrix molecules) are involved in the formation of spatial and temporal associations in the microenvironment of stem and progenitor cells.

Local tissue damage leads to the formation of new niches for stem and progenitor cells, qualitatively different from those in intact tissue, where there is a natural physiological updated pool of these cells. This distinction is extremely important in the strategy of cell phenotype specialization in normal and damage-induced microenvironment. Not so long ago was open common to all types of adult stem cells the ligand-receptor system (SCF / c-kit), mediating the process of early stages of stem-spaces cells reactivation (Thorgeirsson S.S., 1996).

Dimensions of stem-spaces and age. After completion of the embryonic period the role of stem cells is limited to physiological requirements of the organism in renewal of the cells composition and implementation of compensatory function in violation of the tissue completeness. With the onset of postnatal ontogeny quantityof stem cells is gradually reduced. In particular, its shown reduction of mesenchymal stem cells osteogenic potential with the achievement of a minimum level already to the age of 40 and cartilaginous tissue initially characterized by a limited reparative potential, apparently due to local shortages of mesenchymal progenitor cells and growth factors. Assumed, that the progenitor mesenchymal cells precommitive to chondrogenesis enter into the cartilaginous tissue from other stem sources (Sukhikh G.T. et al., 2002).

In the adult organism at equilibrium state of hemo- and lymphopoiesis stromal cells of bone marrow and lymphoid organs are updated very rarely and significant restructuring of stromal structures in these organs does not occur. In an experimental model for studying of bone marrow regeneration using a mechanical devastation of tubular bones medullary cavity — curettage. Therefore in the regeneration process involves not only populating the damaged organ of hematopoietic or lymphoid elements, but also its stromal structure. By existence, creates new stromal areas which repopulates by hemopoietic stem cells.

Application of the method of selective cloning allowed performing quantity estimation of hematopoietic and stromal-precursors populations, and studying changes in their numbers while elimination of hematopoietic tissue from a state of dynamic equilibrium. About the intensity of hemopoiesis, authors arbitrated by the number of hematopoietic cells, and by the concentration and quantity of stromal cell precursors — about the ability of bone marrow to form stromal structures. Established, that the recovery rates between hematopoietic and stromal cells have no direct correlation. Increase in the population of stromal precursors occurs at an earlier date after curettage, and stromal fibroblasts themselves become phosphatase-positive, which is characteristic of osteogenic tissue. Curettage of 3–5 tubular bones leads to an increase of this cells population in the bone marrow of non-operated bones and even in the spleen. At 20 days the number of hematopoietic elements is only 68 % of the control level, while the number of colony-forming fibroblast cells significantly increases (Gerasimov Y.V. et al., 2001). In femoral fractures for the 60th day of the prolonged osteosyntesis the concentration of clonogenic stromal mechanocytes in the area of bone regeneration is increased compared with control by 11 times, and their numbers increased by 6 times. However, the number of myelocytes in the operated and contralateral bones decreased by 26 and 40% (Ilizarov G.A., Burke V., 1980; Ilizarov G.A. et al., 1980).

These data stands under doubt of the bone marrow hematopoietic stem cells to unlimited self-renewal ability. N.I. Drize and colleagues have shown that in irradiated mice reduced by hematopoietic cells transplantation hematopoiesis maintained throughout all life by many tens of simultaneously functioned small and short-lived clones. Short period existence of clones suggests that hematopoietic stem cells are not capable to have prolonged self-renewal and have limited proliferative potential. To confirm the validity of this conclusion, the authors analyzed the clonal composition of the mice bone marrow after transplantation of various doses of hematopoietic cells containing unique genetic markers as a result of human gene adenosine deaminase integration. It is shown, that reducing the dose of donor hematopoietic cells accelerates hematopoietic reversion to the recipient type and decreases the number of functioning clones. Since the results of this study confirms the failure of hematopoietic stem cells to prolonged self-renewal and proved its limited proliferative potential, authors have recommended to transplant maximum greatest number of hemopoietic stem cells (Drize N.I. et al., 1997).

It was established that the content of stromal clonogenic cells in the hematopoietic and lymphoid organs of mice and guinea pigs reduces with age. The most significant reduction in their number is observed in the thymus of mice and guinea pigs, as well as in the spleen of mice — by more than 12, 75 and 8 times respectively. In the bone marrow of old mice and guinea pigs were observed twice, and in the spleens of older guinea pigs — by 40 % drop of the stromal clonogenic cells content in compared with young animals. The obtained data is ensuring proved reduction in the quantity of determined and inducible osteogenic precursor cells during aging (Friedenstein A.J. et al., 1999). In vitro stromal precursor cells giving large colonies in primary cultures, maintains no more than 34 doublings, and with an increase in the level of doubling the

percentage of large colonies is reduced (Chailakhyan R.K. et al., 2001).

Unlike human, rodent cells retain throughout life a high telomerase activity in many tissues, including liver (Tsujiuchi T. et al., 1998). Nevertheless, in old animals a significant part of unipotent hepatocytes population loses the ability to enter into the cells cycle in response to a mitotic stimulus (Uryvaeva I.V., 2001).

De novo formation of neurons in the neocortex, hippocampus, striatum and septum of the mature brain (Kirschenbaum B.M. et al., 1994; Palmer T.D. et al., 1995; Pincus D.W. et al., 1998; Gould E. et al., 1999; Kukekov V.G. et al., 1999; Scharff C., 2000) actually evidences about the existence of dormant (reserve) stem and progenitor cells capable to proliferation with the generation of nerve and glial cells during changes in functional status and pathology of the CNS. Numerous studies results indicate that the enriched environment, learning, intense locomotor activity, as well as some pathological changes in the brain stimulate the formation of new neurons in dentate gyrus of the hippocampus, contribute to the formation of long-term potentiation in the hippocampus and improves cognitive functions (Kempermann G. et al., 1997; Gould E. et al., 1999; Kempermann G., Gage F., 1999; Nilsson M. et al., 1999; Van Praag H. et al., 1999; Gould E. et al., 2000), including while aging (Cameron H.A., McKay R.D., 1999; Kempermann G. et al., 1998). However, with ageing the intensity of neurogenesis decreases, although retained in the mature and aging brain of rodents and primates including humans (Altman J., Das G.D., 1965; Eriksson P.S. et al., 1998; Gould E. et al., 1999; Kempermann G. et al., 1998; Roy N.S. et al., 2000).

We share the view L.I. Korochkin who believes that the discovery of neural stem cells did not abolish the basic positions of the existing paradigm in neurobiology as well as the fact that the nervous system has limited ability to regenerate has been known before, and postulate failure to mature nerve cells to divide the results of stem cell research does not refute. In addition, the nervous system is not «stuffed» with stem cells, and has a very limited number of centers that contain them (Korochkin L.I., 2001).

In principle, the model of induced reduction of stem-spaces sizes already exists. This is the model of accelerated aging in experimental animals suggested to study geroprotective effects of new drugs (Frolkis V.V. et al., 2002). Its essence concludes in the 2 Gy radiation exposure doses of mature animals. It is believed that while there are persistent changes in chromatin structure and protein synthesis in cells, DNA breaks, mutations and chromosomal aberrations, which leads to premature aging of cells, and with it a multicellular organism. But it is well known that the radiation factor is substantial inducer of apoptosis, and not only individual cells, but entire regions of the cell, which should cause the recruitment cells of stem-spaces and consequently, reduce their size. The result of such reduce stem-spaces — premature aging of the animals.

Thus, literature data suggest an important fact — the size of the stem-spaces and proliferative potential of adult regional stem cells are limited. Therefore, to achieve the amplification effect of regeneration of aging cells or rather to replace the old cells pool by young cells, the stem space required to be expanded by stem cells introduction from outside sources. In this respect are very interesting data about that genetically modified clones and cell lines of neural stem cells embedded in multiple areas of the CNS of adults and even of the aging recipients, demonstrating the capacity for adequate integration and differentiation. But most significantly includes that some neural stem cells remain pluripotent after intracerebral transplantation (Sukhikh G.T., Malaytcev V.V., 2001). This means that exogenous stem cells can be included in the stem-spaces of the recipient and to expand its. In particular, the population of the liver parenchyma by exogenous unipotent hepatocytes, introduced into the bloodstream in the form of suspensions, is just as integration — growing of new cells in the free zone of lobules girder structure ensures the preservation of the normal liver cytoarchitectonics (Braun K.M., Sandgren E.P., 1998; Overturf K. et al., 1997).

Estabilshed that behind-barriers located brain of adult animals, the transplanted cells migrate, differentiate and engraftment without any apparent immune response from the recipient organism (Aleksandrova M.A. et al., 2001). However, the expansion of other stem-spaces of the body is only possible when the control antigen homeostasis system was reinstalled, otherwise expression of major histocompatibility complex molecules in differentiating cells leads to a rejection of cells transplants (Royt A. et al., 2000; Down J.D., White-Scharf M.E., 2003). Reprogramming

of the immune system by using high doses of EPC not only allows to perform cell transplantation without subsequent long-term use of immunosuppressive drugs, but also opens up entirely new prospects for increasing longevity and exceeding human life quality.

According to one of the main position of the adaptive-regulatory theory, aging is genetically determined features of the living systems organization (Frolkis V.V., 1998). We consider that these features are determined by the size of stem-spaces, diversity of which can be easily explained heterochrony, heterotopic, heterocateftenic and heterokineticy of aging process. The remaining positions of aging adaptive-regulatory theory are fully consistent with the fourth postulate of the depletion of stem-spaces theory (after depletion of stem-spaces cells reserves intensity and the speed of a multicellular organism aging is determined by the mechanisms of somatic differentiated cells aging within the Hayflick limit).

We propose three basic principles of using cells technology to rejuvenate the body and prevention of aging:

1. Expansion must be applied to all stem-spaces of the aging organism.

2. For the effective houming of exogenous stem cells, the required conditions are preparation of stem-spaces of the recipient to create niches that arise on the site of apoptosis, which is achieved by using generalized pressing on energy systems of senescent cells by hypoxic and hyperoxic stress.

3. For expansion of the body stem-spaces by cells transplantation requires the use of high doses of embryonic progenitor cells capable to substitute the recipient's immune system.

As follows attention to be paid on unpredictability result of the cell transplantation in oncological diseases, when the introduction of stem cell seems to be very dangerous because their differentiation can occur under the influence of the microenvironment factors which generates by tumor that poses a real threat not only to accelerate the growth of neoplasms, but also intensive metastasis even those tumors, which are characterized by predominantly invasive growth.

There is another version of the regenerative medicine — Tissue Therapy, which is based on the effects of protein and non-protein molecules of allo- or xenogenic origin parabiotic tissues (Filatov V.P., 1952). In our opinion, the basic principle mechanism of tissue therapy is based on the effect of retrospective action of oligopeptides on the cell's genome. It is known that peptide bioregulating molecules are formed by limited proteolysis and have a broad spectrum of biological activities, coordinating the processes of biosynthesis in cells by influencing on the expression of specific gene sequences (Khavinson V.H., 2001). Attention paid that the practicaly entire process of embryogenesis is built on the subsequent action of peptide regulators (growth factors, cytokines) in the genome of embryonic cells (Khavinson V.H., Malinin V.V., 2002). Proved, that particularly microenvironmental factors determine the direction of migration and further differentiation of embryonic stem and progenitor cells (Repin V.S., Sukhikh G.T., 1998).

We consider that this is why the use of tissue-specific proteins, some of which have already been allocated to the «pure» form, or synthesized, is effective in the treatment of chronic diseases like asthma, arthritis, congestive heart failure, endarteritis obliterans, trophic ulcers and others. It is established geroprotective effect of such tissue-specific protein preparations, as epithalamin, epithalon, timalin, vilon, cortexin, retinolamin, prostatilen, prostamaks and livagen (Khavinson V.H., 2001; Khavinson V.H., Malinin V.V., 2002).

Thus, experimental and theoretical stages in the development of regenerative medicine has already given the scientific reasons for exit into practice, however realize the tremendous potential of cells transplantation and tissue therapy is necessary and is very important to consider all theoretical achievements and inclined world clinical experience to minimize the propability of side effects and achieve positive results of treatment.

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СТАРЕНИЕ: ТЕОРИЯ ИСТОЩЕНИЯ СТВОЛОВЫХ ПРОСТРАНСТВ ТЕЛА

В обзоре проанализирована основная информация о принципах и методах нового направления в лечении больных, именуемого регенеративной медициной, основная информация о стволовых пространствах организма, содержатся данные об истощении ресурсов стволовых клеток при старении и представлена собственная теория механизмов старения.

Ключевые слова: *стволовые клетки, стволовые пространства, иммунная система замены, старение, регенеративная медицина.*

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СТАРІННЯ: ТЕОРІЯ ВИСНАЖЕННЯ СТОВБУРОВИХ ПРОСТОРІВ ТІЛА

В огляді проаналізована основна інформація щодо принципів і методів нового напрямку в лікуванні хворих, який має назву регенеративної медицини, основна інформація щодо стовбурових просторів організму, містяться дані про виснаження ресурсів стовбурових клітин при старінні і представлена власна теорія механізмів старіння.

Ключові слова: *стовбурові клітини, стовбурові простори, імунна система заміни, старіння, регенеративна медицина.*