REVIEW OF REPORTS OF THE 13th MEETING OF THE INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH – ISSCR (24-27 June 2015, Stockholm, Sweden)

24-27 June 2015, Stockholm (Sweden) hosted the 13th annual meeting of the International Society for Stem Cell Research – ISSCR.

The plenary sessions of the conference were devoted to the following subjects:

- Disease modeling
- Creation of tissues and organs
- Immunology and Stem Cells
- Pluripotency, reprogramming mechanisms
- Regeneration and engraftment
- Stem cell therapy

The congress was held under the following thematic sessions: actual issues of cell activity, in particular the processes of cell adhesion and migration; control and induction of pluripotency, transdifferentiation, reprogramming and regulatory stem cells networks; hematopoiesis; epithelial and mesenchymal stem cells (MSCs), stem cells from nervous system, pancreas, lung, liver, intestine and cancer stem cells; disease modeling; ethical aspects of stem cells.

The presidential symposium «Manipulating stem cells in development and disease» took place within current ISSCR conference. The presidential symposium was lectured by the world's leading scientists, including Professor. Fred H. Gage (Salk Institute For Biological Studies, USA), Prof. Jurgen Knoblich (Institute of Molecular Biotechnology, Austria), prof. Shinya Yamanaka (Kyoto University, Japan and University of California, San Francisco, USA).

Scientists Irving Weissman (Stanford School of Medicine, USA) and Hans Clevers (Hubrecht Institute, Netherlands) at the 13th meeting of ISSCR received a prestigious McEwen Award for Innovation from the McEwen Centre for Regenerative Medicine (Toronto, Canada) for original thinking and pioneering studies of stem cells and regenerative medicine. A scientist Alan Trounson (MIMR-PHI Institute of Medical Research, Australia) was awarded the Public Service Award. Dr. Alan Trounson earned recognition for his pioneering work on in vitro fertilization and other reproductive technologies.

One of the honorary speakers of the conference was prof. Shinya Yamanaka, winner of the Nobel Prize in Medicine and Physiology in 2012 for his discovery of induced pluripotent stem cells. Currently, prof. Shinya Yamanaka heads the Center for Research and Application of iPS-cells at the University of Kyoto (Japan), and is a senior researcher at the Gladstone Institute of Cardiovascular Diseases in San Francisco (USA). In the presidential symposium prof. Shinya Yamanaka gave a lecture «Recent advances of iPS-cells application». Professor pointed out that the induced pluripotent stem cells (iPS) have unlimited capacity to differentiate into different lines. This made them an invaluable tool for cell therapy, disease modeling and research of medicines. Today, scientists optimized application technologies of induced pluripotent stem cells in regenerative medicine, having reached reduced tumorogenicity. In 2014, the world's first clinical trial on the use of induced pluripotent stem cells was announced, in which retinal pigment epithelium derived from induced pluripotent stem cell was transplanted to patients with age-related macular degeneration. Scientists suggest that induced pluripotent stem cells will be even more widely used in medicine in the near future. So, in the coming years clinical studies on the use of induced pluripotent stem cells to treat Parkinson's disease and thrombocytopenia are expected. Also a commercial project on launching of the bank of clones of induced pluripotent stem cells from donors with homologous HLA-phenotype was initiated. The use of such clones implicates the reduction of the immune response and risk of transplant rejection. Other vectors of application of induced pluripotent stem cells include a study of new drugs, research on toxicity and study of the mechanisms of diseases. Also, induced pluripotent stem cells may be used for prophylactic purposes since these cells may help to predict patient's condition and prevent the development of certain diseases.

At the plenary session «Regeneration and Engraftment» prof. Jonas Frisen (Sweden) gave a lecture «Adult neurogenesis in humans». It is known that in most mammals, neurons are able to regenerate in the area of olfactory bulbs and the hippocampus. Generation of neurons in the adult brain maintains a pool of nerve cells with unique properties. It is known that neurogenesis decreases with age and the possibility of recovery of neurons in humans for a long time has been a subject of many scientific debates. Scientists presented the results of histochemical studies of neurogenesis in adults. Thus, it is shown that hippocampal neurons regenerate throughout the life of man. People are unique because in humans differently from other mammals neurogenesis is not detected in the olfactory bulbs. Current study is of great importance for the understanding of the fundamental processes of regeneration of nerve tissue in humans and creation of prerequisites for regenerative therapy of neurodegenerative diseases.

Prof. Kari K. Alitalo et al. (Finland) presented a very interesting paper «Targeting endothelial growth factor pathways in cancer and cardiovascular disease». In recent years scientists accumulated numerous data on the molecular mechanisms of angiogenesis, that is especially important for manipulation of the processes aimed at the treatment of cancer and ischemic diseases, the creation of pro-angiogenic and anti-angiogenic drugs. Scientists have even made several attempts to stimulate neoangiogenesis. However, in many pathological processes, such as inflammation, metastasis, immune system dysfunction limphoangiogenic growth factors are involved. Research and manipulation of secretion of limphoangiogenic growth factors may have therapeutic value in the treatment of several diseases.

Dr. Mohammed Al Bagami et al. (France) in the paper «Comparison between healthy donor derived bone marrow mesenchymal stem cells: and human dermal fibroblasts: impact on clinical applications of MSC» analyzed the phenotype and functional properties of MSCs from bone marrow and human dermal fibroblasts. Proposed parameters of differentiation of these populations of cells, especially the gene expression profile, are important for the evaluation of contamination of the bone marrow by fibroblasts, what may result in unpredictable effects of the therapeutic use of MSCs from bone marrow.

Dr. Anna Badner et al. (Canada) presented the report «The vasoprotective effect of early intravenous mesenchymal stromal cell delivery after traumatic spinal cord injury». The effectiveness of the early systemic infusion of MSCs on a model of spinal cord injury in rats was investigated. It was shown that this treatment significantly reduces the pathological manifestations and progression of the disease, although the mechanism of the positive effects of stem cells in spinal cord injury is not fully under-

stood. Use of stromal cells isolated from umbilical cord tissue and fetal brain caused the decrease of vascular permeability and reduce of hemorrhages and lesions area. However, cell engraftment in spinal cord tissue was insignificant. Scientists have concluded that this therapeutic effect is due to the multiple trophic factors, secreted by the infused stem cells.

Noteworthy is the report of Dr. Alix Kay Berglund et al. (USA) on the theme TGF-beta-2 decreases surface expression of MHC-1 on equine bone marrow-derived mesenchymal stromal cells. Mesenchymal stromal cells from bone marrow have been widely used in the treatment of musculoskeletal diseases, but it is shown that incompatibility according to MHC-1 system between the donor and recipient may lead to immunological complications. Therefore, scientists have developed a method of molecular manipulation of MSCs to create in immune-privileged graft, one of which is the use of the culture of stem cells with TGF-β2.

Dr. Emma Board-Davies et al. (Sweden) presented a promising paper «Oral mucosal lamina propria progenitor-cells display broad spectrum antibacterial properties via the secretion of osteoprotegerin». It is well known that stem cell precursors isolated from the mucous membrane of the oral cavity are a new population of stem cells with pronounced immunosuppressive properties and the possibility to inhibit the proliferation of lymphocytes, the latter was characterized by a dose- and contact-dependent character. However, in this study colleagues showed revolutionary data that stem progenitor cells isolated from the mucous membrane of the oral cavity, can significantly reduce the growth of bacteria.

The study of the biological properties of dental pulp MSCs was presented by Dr. Annelies Bronckaers (Belgium) et al. entitled «Unraveling the angiogenic properties of human dental pulp stem cells in vitro and in vivo». Stem cells of the pulp of the teeth are easy to isolate, cultivate and cryconservervation, they also represent an attractive source of material for cell therapy. In this paper the angiogenic properties of mesenchymal stem cells from dental pulp were investigated. It was shown that these cells secrete both pro- and anti-angiogenic factors, such as vascular endothelial growth factor (VEGF), monocyte chemotactic protein-1 (MCP-1), endostatin. Effect of the dental pulp MSCs on the processes of proliferation and cell migration – the key stages of angiogenesis was studied. It has been shown that dental pulp mesenchymal stem cells stimulate angiogenesis by paracrine mechanism and, therefore, can serve as an important cellular material for tissue engineering purposes and treatment of diseases that are accompanied by insufficient angiogenesis.

Dr. Campos de Carvalho et al. (Brazil) presented unique data on the effect of autologous bone marrow MSCs on the functional parameters of the cardiovascular system of dogs infected by Trypanosome cruzi in the chronic phase. The researchers concluded that treatment with stem cells leads to improved functional activity of myocardium in heart damage, caused by Trypanosome cruzi infection, however, this effect was not observed in case of application of allogeneic cells.

Dr. Giuliana Castello Coatti et al. (Brazil) presented a report «Human adipose derived pericytes increase survival in an ALS mouse model but only in affected males». Despite contradictory results of pre-clinical research aimed at the treatment of amyotrophic lateral sclerosis with MSCs, it is known that these cells possess immunosuppressive and neuroprotective effects, reduce the manifestations of oxidative stress, what creates a theoretical background for cell therapy of this disease. Pericytes are a more homogeneous cell population, and in addition to the paracrine secretion of a number of factors these cells have a unique advantage – the ability to maintain the blood-brain barrier, what is important in neurodegenerative diseases. On a model of amyotrophic lateral sclerosis in mice therapeutic effect of pericytes and culture of mesenchymal stem cells derived from human adipose tissue was investigated. Interestingly, male mice showed a better therapeutic effect in response to treatment.

Dr. Caroline E. Gargett et al. (Australia) presented a report «Culture expansion of undifferentiated human endometrial MSC using a small molecule inhibitor». Endometrial mesenchymal stem cells are a new source of stem cells, extracted from the inner lining of the uterus – the endometrium, which has an extremely high regenerative potential. The report provides the possibility of using inhibitor of small molecules, such as A83-01, for the expansion of endometrial MSCs for tissue engineering.

Andrew Pullin et al. presented an interesting report «Tissue-engineered bone grafts for maxillofacial surgery: from bench to bedside» in which colleagues shared clinical experience of mesenchymal stem cells application for tissue engineering in dentistry. Scientists have used synthetic tricalcium phosphate scaffolds and autologous stem cells (multipotent gingival MSCs; vascular fraction of adipose tissue) in order to create different tissue-engineered structures. Obtained tissue-engineered structures were transplanted as bone grafts to patients to increase the maxillary gingiva as a first stage of dental implantation. Currently, 4 patients have been treated by this technique. No postoperative complications were noted as well as no side effects of the conducted surgical treatment were observed. According to trial, 3-6 months after treatment heteromorphous regenerate in timely adherent to the surrounding bone tissue was noted. Density of regenerate slightly exceeded the parameter of the intact trabecular bone. Newly formed bone was confirmed by histological examination of bioptate. Clinical trials are ongoing.

«Avoiding lower extremity amputation: cell therapy of critical ischemia of the limbs. Design and interim results of four clinical trials» so was the title of the report of the group of scientists Soria Bernat et al. from Spain. Amputation of the lower extremities is a major complication of diabetes mellitus, which leads to a significant reduction in the quality of life of patients and high mortality. It is known that intra-arterial infusion of bone marrow mononuclear cells is successfully applied in the treatment of critical limb ischemia. The authors of this study in their presentation spoke about the current 3 randomized and controlled clinical trials, launched to learn more about this method of treatment.

As part of the clinical trials, patients underwent intra-arterial infusion of autologous mesenchymal stem cells of adipose tissue in 2 doses ($0.5 \cdot 10^6$ cells/kg and $1 \cdot 10^6$ cells / kg body weight). Also, another group of patients were infused $150\text{-}250 \cdot 10^6$ autologous bone marrow mononuclear cells, or autologous cells $2\text{-}7 \cdot 10^6$ $CD133^+$, or $0.5 \cdot 10^6$ cells/kg of autologous MSCs. Intra-arterial infusion of stem cells was performed to 48 patients with type 2 diabetes mellitus with critical limb ischemia. Dynamic monitoring of patients included an assessment of the safety and efficacy of the treatment, as well as the determination of insulin resistance and insulin requirements. 12 months after treatment, all patients showed a significant improvement according to the Rutherford-Becker classification, wounds scale of the University of Texas and ankle-brachial index. Clinical improvement was associated with neoangiogenesis processes, confirmed by digital angiography.

Sabena Sultan et al. (UK and Greece) presented a promising paper «Immunomodulatory progenitor cells: a novel allogeneic therapy for patients with ischemic cardiomyopathy undergoing coronary artery bypass grafting». Immunomodulatory progenitor cells is a new definition for mesodermal cells precursors, but not mesenchymal stem cells, approved by the International Society for Cellular Therapy. Immunomodulatory progenitor cells are characterized by the immunomodulatory phenotype (MIC A/B, CD178, CD289, CD99 and EGF-R) and specific cardiac markers (CD181, CD126, CD304, CD363 and CD182).

Allogeneic immunomodulatory progenitor cells were used in phase II clinical trial Heartcel in patients with decompensated heart failure not revascularized by coronary artery bypass. A clinical study Heartcel was performed in 2014. Immunomodulatory progenitor cells were injected intramyocardially into the foci of hypokinetic myocardium. As a result of treatment, clinical and statistically significant improvement was observed, in particular increase of the left ventricular ejection fraction LVEF (30 %), reduction of the size of the scar of the left ventricle (40 %) and improvement of the quality of life of the patient (50 %).

Dag Josefsen et al. (Norway) in the report «Clinical application of human adipose derived regenerative cells (ADRCs) in tissue repair of severe side effects following curative radiotherapy treatment». Actually treatment of post-radiation wounds includes methods of plastic surgery and, if indicated, hyperbaric oxygenation. But, as it was revealed recently,

injections of adipose tissue stem cells directly into foci of chronic wounds accelerates tissue healing. Regenerative cells of adipose tissue, also known as the stromal vascular fraction, contain endothelial progenitor cells, smooth muscle cells and adipose tissue derived cells. Today only a small number of patients with injuries worldwide passed this treatment, but the results of conducted therapy gives reason to believe that such treatment is promising and can be considered as an alternative to conventional treatment. As it was emphasized by the researchers, the procedure of isolation of stem cells from adipose tissue is well established, safe and makes it easy to get a large number of cells. It was found that one gram of adipose tissue contains 300-500-fold more stem cells than bone marrow.

Aurore Lafosse et al. (Belgium) presented a paper «Impact of diabetes on dermal fibroblasts and keratinocytes: potential of adipose-derived stem cells in cell therapy for chronic diabetic wounds», in which discussed an important problem of cell therapy, namely, how the disease affects the properties of stem cells and the availability of stem cells in the adult patient for autologous therapy. It is known that with age and under pathological conditions clonogenic and proliferative potential of stem cells is reduced, such cells due to their biological potential yield cell material obtained from young healthy donors. In this presentation scientists confirmed in studies in vitro that skin fibroblasts are very sensitive to hypoxia and hyperglycemia, the latter always occur in the case in diabetes. However, scientists have shown that adipose stem cells may well survive in adverse conditions of diabetes and presented clinical experience of treatment of patients with type 2 diabetes using biological dressings containing adipose stem cells.

Anish Sen Majumdar (India) presented the poster «Efficacy of Stempeucel®, an allogeneic pooled human mesenchymal stromal cells, in multiple preclinical models of human diseases with diverse pathophysiology,» in which they introduced a cell's drug, developed by them. Stempeucel® is a drug of allogeneic human MSCs from different healthy donors, which is produced under GMP conditions. Currently stromal/stem cells from bone marrow are studied extensively in basic and translational research. It was found that stromal/stem cells from bone marrow have potent immunomodulating and anti-inflammatory properties and stimulate tissue regeneration and angiogenesis by secretion of trophic factors. The ability of the stromal/stem cells of the bone marrow to influence functional properties of almost all types of immune cells in a paracrine mechanism, and through interaction with cell surface targets expanded the use of these cells in the allogeneic transplantology. Scientists hope that the biological product they created will find its niche in regenerative medicine.

Catarina Oliveira Miranda et al. (Portugal) in the report «Transplantation of mesenchymal stromal cells alleviates motor impairments and neuropathology of a mouse model of Machado-Joseph disease» presented a new approach to the treatment of this disease with the use of transplantation of MSCs. Machado-Joseph disease or ataxia type 3 is the most common spinocerebellar ataxia in the world, a genetically mediated disease. It was shown that transplantation of mesenchymal stem cells reduces manifestations of Machado-Joseph disease and can be considered as a new effective treatment for this still incurable disease.

Anna Maria Ranzoni et al. (Australia) presented a paper «Neonatal transplantation of human amniotic fluid stem cells improves bone quality in a mouse model of osteogenesis imperfecta.» Osteogenesis imperfecta is a congenital disease that occurs with a frequency of 1:10000 children and manifests with bones fragility. Among the methods of treatment of osteogenesis imperfecta scientists consider the possibility of prenatal transplantation of MSCs capable to differentiate into osteoblasts. Fetal human mesenchymal stem cells can be obtained only from amniotic fluid in the middle period of gestation. In the present study, the stem cells of human amniotic fluid were injected to newborn mice with osteogenesis imperfecta, 8 weeks later the animals were examined. It was noted that in mice, who received treatment with stem cells, fractures frequency was lower than in untreated mice. Frequency of femur fractures was 3.6 % versus 33 %; tibia 3.6 % vs. 17 %. Therapeutic effect of transplantation of MSCs researchers explained by the fact that the maturation of the transplanted progenitor cells into preosteoblasts directly or indirectly enhances mineralization and bone quality.

Eric Neely et al. (Canada) presented the report «Development of local acting biologics for combined stem cell and gene therapy to treat arthritis». Rheumatoid arthritis is an autoimmune disease that is characterized by chronic inflammation, joint damage and decreased quality of life of the patient. In rheumatoid arthritis, an increased production of proinflammatory cytokines occurs, in particular tumor necrosis factor alpha, which stimulates the proliferation of immune cells, production of other proinflammatory cytokines, what ultimately leads to joint damage. Currently only remedies of systemic action are available for the treatment of rheumatoid arthritis, and this treatment is accompanied by side effects – decrease of immunity and thus increased susceptibility to tuberculosis and an increased risk of tumors development. The authors presented a new biological drug known as TNF-α «sticky traps».

In Ukraine, Institute of Cell Therapy is a member of the International Society for Stem Cell Research and at the 13th ISSCR meeting in Stockholm Ukraine was represented by the director of the Institute cryobank Galina Lobyntseva, Ph.D., winner of the State Prize of Ukraine and Volodymyr Shabliy, PhD, deputy director of cryobank. Researchers of the Institute of Cell Therapy also presented 3 research reports.

The poster «Transplantation of placental adherent cells does not affect mid/late tumor progression in dimethylhydrazine-induced colon carcinogenesis in rats» presents unique data on the evaluation of the biological properties of placental stem cells and perspectives of their application in the treatment of malignant tumors. Colorectal cancer is one of the most common forms of cancer, which is rarely detected in the early stages. With the development of modern science researchers and clinicians are considering new, more effective approaches to the treatment of this disease, including cell therapy. Stem cells of the placenta are considered to be especially promising for the treatment of malignant diseases the as placenta is not a favorable niche for cancer cells. Ukrainian scientists studied the effect of intravenous infusion of placental multipotent cells in dimethylhydrazine-induced colorectal cancer in rats. Placental stem cells were administered to rats at a time when each animal developed at least one adenocarcinoma. It has been shown that cell cultures derived from placenta, have the properties both of mesenchymal stem cells and trophoblast stem cells, expressing markers CD90, CD29, CD44, but did not express CD45. Also investigated placental stem cells had the capacity to differentiate into adipogenic and osteogenic lines. In the course of treatment decrease in the number of lesions and size of tumor were observed. It was also shown that placental stem cells do not promote early or late tumorogenesis. Transplantation of placental adherent cells does not affect mid/late tumor progression in dimethylhydrazine-induced colon carcinogenesis in rats.

Another reports of Institute of Cell Therapy were «Hematopoietic stem/progenitor cells from human placental tissue, umbilical cord blood and fetal liver» and «Placental derived multipotent cells possess trophoblast specific features».

Analysis of the reports presented at the conference of the International Society for Stem Cell Research states that most of presented research is of a translational character, i.e., running studies are directed at the indispensable implementation of new developments into medical practice, as well as significant clinical advances in regenerative medicine within the last decade are noted.

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