МЕСТО ОДРЖАВАЊА: АМФИТЕАТАР МЕДИЦИНСКОГ ФАКУЛТЕТА У КРАГУЈЕВЦУ
ТРАЈАЊЕ ПРОГРАМА И АКРЕДИТОВАН БРОЈ ПОЕНА:
Симпозијум траје један радни дан, са укупно 7 часова активне наставе
На основу одлуке Здравственог савета број 153-02-489/2011-01 од 15. 09. 2011. године, евиденциони број А-1-3029/11, симпозијум је акредитован са 9 бодова за слушаоце.
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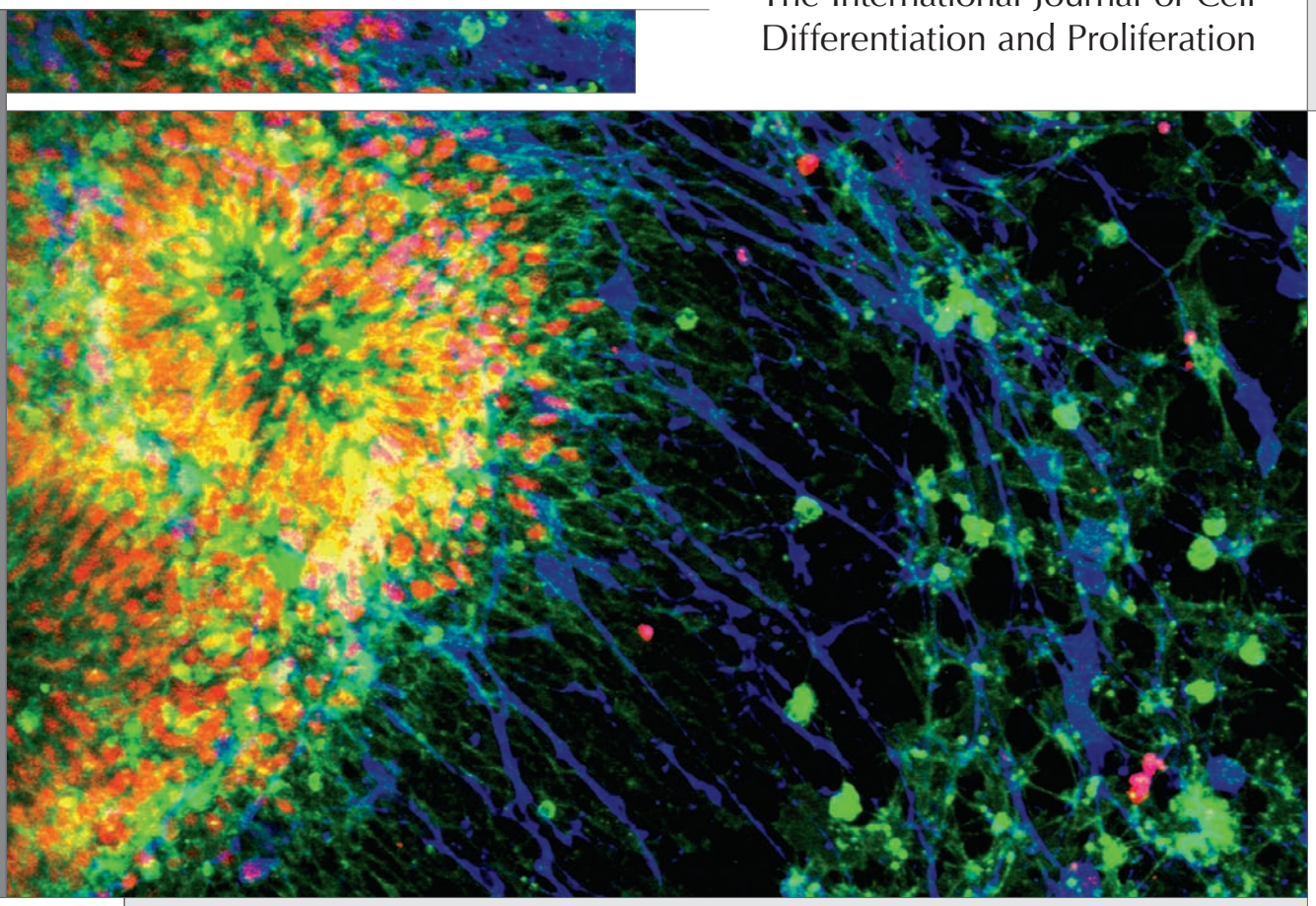

The Stem Cell Symposium

October 15, 2011

In Partnership with the City and Universtirty of Kragujevac Serbia

University of Kragujevac

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Scientific Program

Welcome: Veroljub Stevanovic, Mayor of Kragujevac, Slobodan Arsenijevic, Chancellor of University, Nebojsa Arsenijevic, Dean of Medical Faculty **9.00-9.10**

Miodrag Stojkovic **9.10-9.15**

Short introduction to stem cells

Hans Schoeler **9.15-9.45**

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Induction of pluripotency in germline and somatic stem cells

The mammalian germline comprises the inner cell mass (ICM) and epiblast, containing pluripotent cells, and the germ cell lineage, hosting unipotent cells. Embryonic stem (ES) cells, derived from preimplantation embryos, comprise two cell types with divergent states of pluripotency. Similarly, epiblast stem cells (EpiSCs), derived from postimplantantion embryos, comprise cells of early and late pregastrulation embryos.

The ultimate goal of cell and developmental biology is to program cells at will. The first step in converting any given cell type into another cell type is to achieve a pluripotent stem cell state that resembles that of ES cells. Somatic cells need exogenous transcription factors to achieve pluripotency. Reprogramming of mouse and human somatic cells into pluripotent stem cells, termed induced pluripotent stem (iPS) cells, was first described in 2006 using fibroblasts (somatic cells) and initially required the virally-expressed transcription factor quartet of Oct4, Sox2, c-Myc, and Klf4. Later, we reported that Oct4 alone is sufficient to directly reprogram adult mouse and human fetal neural stem cells (NSCs) into iPS cells, showing that Oct4 plays a crucial role in the reprogramming process. We recently showed that induced EpiSCs (iEpiSCs) can be obtained by directly reprogramming somatic cells with the quartet under EpiSC culture conditions.

In contrast to somatic cells, primordial germ cells (PGCs) were first induced to pluripotency 20 years ago by the mere modulation of the culture conditions. We recently converted adult germline stem cells (GSCs) into germline-derived pluripotent stem (gPS) cells. GSCs are unipotent testis cells capable of not only self-renewing, but also giving rise to sperm. Like ES cells, GSCs exhibit significant levels of Oct4 and Klf4, but low levels Sox2 and c-Myc.

To better understand the reprogramming process, we sought to identify factors that mediate reprogramming with higher efficiency. We established an assay based on *Oct4* reactivation to screen nuclear fractions from extracts of pluripotent cells. BAF chromatin remodeling complexes containing the Brg1 protein enhance the efficiency of quartet-mediated reprogramming of somatic cells to pluripotency. As knockdown of Brg1 leads to differentiation of ES cells, we investigated the early effect of Brg1 knockdown on the expression of key pluripotency factors via RNA interference. We show that Brg1 knockdown leads to immediate *Sox2* downregulation, *Nanog* upregulation, and *Oct4* upregulation, the latter perhaps triggering ES cell differentiation. Our data suggest that Brg1 plays an important role in regulating the expression of Oct4, a factor instrumental in maintaining cellular pluripotency.

Aleš Hampl **9.55-10.25**

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Can we learn about cancerogenesis from embryonic stem cells?

Pluripotent human embryonic stem cells (hESC), early upon their derivation from normal human blastocyst, are considered as genetically undamaged. In consonance with this fact, when implanted to immunodeficient host, hESCs give rise to teratomas containing differentiated cells and not malignant tumors. This may change in hESCs propagated in culture for longer periods of time due to the accumulation of a large spectrum of genetic and epigenetic alterations.

Currently, the concept of cancerogenesis is being proposed and evaluated, in which cells with stem cell properties, tumor-initiating cells (TICs), play a key role. The origin of TICs as well as molecular mechanisms underlying their properties are largely ununderstood. One plausible hypothesis is that acquiring stem-like phenotype, not dissimilar to that of hESCs, is the first step in TIC development that makes these cells more prone to further abnormalization.

Normal somatic cells developed a series of mechanisms to prevent accumulation of changes to their genetic complement with the cell cycle checkpoints being of premier importance. Our recent data document that amplifications of chromosomes typically observed in cultured hESCs are at least in part due to the unchecked misbehavior of centrosomes. In contrast, we have also shown that pathways for sensing and reacting to DNA damage caused by UVC light are fully operational in normal hESCs. Still, these pathways are centered around CDC25A and do not involve p53-driven up-regulation of p21 inhibitor of CDKs, which is typical for somatic cells and may represent a slower but more robust mechanism to stop cycling. Here we have further studied this phenomenon and found that in UVC-irradiated hESCs there is 85 microRNAs that undergo up-regulation about 2 fold and higher. Among them there are also microRNAs from family miR-302 that share a seed sequence with p21-regulating microRNAs. Importantly, p21 protein accumulates in hESCs with artificially down-regulated microRNA-processing protein Dicer1 but introduction of miR-302 into such cells reestablishes their low-p21 phenotype. Together these findings suggest that undifferentiated hESCs use microRNAs to prevent protein p21 from being produced and thus reveal important mechanism by which hESCs prevent canonical G1/S checkpoint pathway from being activated. Whether this regulation is operative in only hESCs or also in other types of stem cells including stem cells of cancers should be investigated.

Coffee break **10.35-11.00**

Majlinda Lako **11.00-11.30**

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Applications of human pluripotent stem cells for understanding our early development and disease

My group's research is focused on three key stem cell areas, namely: (***i***) understanding of self renewal in human pluripotent stem cells; (***ii***) generation of functional and transplantable blood cells from human pluripotent stem cells and (***iii***) clinical translations of our basic biology studies to treat corneal and retinal blindness. In today's talk I will concentrate on key issues that we face with respect to development of defined transplantable cell types for clinical applications from human pluripotent stem cells. Over the last 5 years we have been able to establish a very efficient model of human ESC differentiation to haematopoietic lineages and retinal photoreceptors cells. Using this differentiation model, we have established a transcriptional network which we are using to understand the role of key transcription factors and miRNAs that govern directed differentiation. Using this molecular signature, we can discuss how similar these cells are to the ones that are found in equivalent niches in the adult. One of the most fascinating aspects of stem cell development in the last four years has been induction of pluripotency in differentiated cells. My group in collaboration with Dr Lyle's Armstrong's group has now established more than 100 iPSC lines using various integrative and non integrative methods. I will discuss how we are using these patient specific cells to understand disease development in early embryos.

Slaven Erceg **11.40-12.10**

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Oligodendrocytes and motoneuron progenitors derived from human embryonic stem cells rescue neurological function in rats with completely transected spinal cord

Spinal cord transection, besides the loss in central control of motor, sensory and autonomic function below the injury site, produces limited exogenous repair and poor functional recovery. The cumulative death of neurons, astroglia, and oligodendroglia in and around the lesion site disrupts neural circuitry and leads to neurological dysfunction Compared with other stem cell types, human embryonic stem cells (hESC) and induced pluripotency stem (IPS) cells currently show the greatest potential for differentiation and cell replacement therapies including spinal cord injury (SCI). These cells are pluripotent and can give rise to cells of three germinal layers. They can be propagated indefinitely in culture and can provide a large quantity of differentiated cells for transplantation including specific cells of neuronal or glial fates. Here we evaluate the therapeutic effects of transplanted hESC-derived oligodendrocyte progenitors (OPC) and/or motoneuron progenitors (MP) on axonal remyelination and functional recovery of adult rats after complete spinal cord transection. OPC and/or MP were grafted into the site of injury in the acute phase. Based on Basso-Beattie-Bresnahan scores recovery of locomotor function was significantly enhanced in rats treated with OPC and/or MP when compared with control animals. When transplanted into the spinal cord immediately after complete transection OPC and MP survived, migrated and differentiated into mature oligodendrocytes and neurons showing *in vivo* electrophysiological activity. Taken together, these results indicate that OPC and MP derived from hESC could be a useful therapeutic strategy to repair injured spinal cord.

Lunch break **12.20-14.20**

Miodrag Čolić **14.20-14.50**

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Immunomodulatory properties of dental mesenchymal stem cells

Adult mesenchymal stem cells (MSCs) have recently become a potent tool in regenerative medicine. Due to certain shortcomings of obtaining bone marrow MSCs, alternate sources of MSCs have been sought. In this work we studied dental (D)-MSCs established from dental pulp (DP-MSCs), dental follicle (DF-MSCs) and periapical dental lesion (PL-MSCs) in order to define differences in their phenotypic properties, differentiation potential and immunomodulatory activities. All cell types showed colony forming ability and expressed typical MSCs markers, but differed in the levels of their expression and functional capabilities. DP-MSCs were more potent in production of transforming growth factor (TGF)-β and suppression of peripheral blood mononuclear cell proliferation, which could be neutralized with anti-TGF-β antibody. The treatment with a Toll-like receptor 3 (TLR3) agonist augmented the suppressive potential of all cell types and potentiated TGF-β and interleukin (IL)-6 secretions by these cells. TLR4 agonists augmented the suppressive potential of DF-MSCs and increased TGF-β production, but abrogated the immunosuppressive activity of DP-MSCs by inhibiting TGF-β production and the expression of indolamine-2,3-dioxygenase(IDO)-1. Some of these effects correlated with higher expression of TLR3 and TLR4 by DP-MSCs compared to other MSC types. The immunomodulatory effects of PL-MSCs were additionally studied on differentiation and functions of monocyte–derived (Mo)DCs. We showed that PL-MSCs inhibited differentiation of monocytes into immature MoDCs, as judged by a slower down-regulation of CD14 and lower expression of CD86 molecules, compared to control MoDCs. In contrast, the presence of PL-MSCs during the maturation of MoDCs with proinflamatory cytokines increased the expression of CD83, CCR7, HLA-DR, CD86, CD40 and CD54. However, such MoDCs up-regulated the expression of ILT-3, ILT-4 and IDO-1 regulatory markers, exhibited lower allostimulatory capacity, produced less IL-12 and IL-10 and more TGF-β, compared to control MoDC. MoDC differentiated and stimulated in presence of PL-MSCs were able induce un-responsive $CD4^+$ T cells and higher percentage of $CD4^+CD25^{high}CD39^+$ regulatory T cells in primary mixed leukocyte reactions, suggesting their tolerogenic function. In conclusion, our results suggest that dental MSCs are functionally different and each of these functions should be further explored in vivo prior to their specific biomedical applications.

Veljko Nikolic **15.00-15.30**

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Cord blood cells and their therapeutic potential in neurodegenerative disorders

Modulation of immune/inflammatory responses by diverse strategies including amyloid-β immunization, non-steroidal anti-inflammatory drugs, and manipulation of microglial activation states has been shown to reduce Alzheimer's disease (AD)-like pathology and cognitive deficits in AD transgenic mouse models. We and others have identified human umbilical cord blood cells (HUCBC) to have unique immunomodulatory potential. Following the multiple low dose HUCBC infusions into PSAPP mice we showed reduced AD-like pathology and rescue of behavioral deficits. With some degree of success, similar HUCBC approach was used in stroke, amyotrophic lateral sclerosis, and Sanfilippo syndrome type B. Generally, there is an evidence of anti-inflammatory effects and secretion of specific cytokines and growth factors that promote cell survival, rather than cell replacement.

Franz Wolfgang **15.40-16.10**

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Regeneration of ischemic cardiovascular diseases: generation, characterization and targeting of cardiovascular stem cells

Abstract not yet provided; reminders sent.

Zoran Ivanovic **16.20-16.50**

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Oxygen stem cell paradigm and its impact on cell engineering

On the basis of more than one-decade long work on hematopoietic stem cells exposed to low O2 concentrations, as well as the ulterior literature data on stem cells (pluripotent, multipotent, tissue-specific), a concept relating the self-renewal with the anaerobic metabolic properties of stem cells and the actual O2 availability is elaborated ("Oxygen Stem Cell Paradigm"). "The Generation-Age Hypothesis", and anaerobic metabolic properties of stem cells are considered in the context of the oxygen-dependent evolution of life and its transposition to ontogenesis and development. The 01"anaerobic", low-energy proliferation seems to be a key of self-renewal: low availability of energy preventing cells from differentiating, which requires more energy than simple cell division uncoupled with differentiation. The latest approaches in ex vivo expansion research exploit these features targeting the regulation of ancestral genes involved in the basic cellular functions (simple proliferation and survival of cells), considered as "stemness/self renewal" factors. Most of these genes are proved either to be activated by a low O2 concentration or to have "Hypoxia Responsing Elements" (HRE) sequence. Our ex vivo expansion procedures (one clinical trial completed and the other ongoing) are based on the principles that the association of a medium with a powerful system of antioxidants with MGDF (Tpo) (stabilizing HIF1α transcripts) mimics the physiological low O2 environment of hematopoiesis. Also, our improvement of ex-vivo Red Blood Cell (RBC) production procedure is based on adaptation of appropriately low oxygenation to each step of culture, enhancing the yield of RBC.

Stem Cells YIA presentation **17.00-17.30**

AWARD **17.40-17.50**

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Adjournment **17.50-18.00**

Accreditation certificates will be issued by the Ministry of Education and Science upon completion of this symposium