The international symposium:

STEM CELLS:

THERAPEUTIC OUTLOOK FOR

CENTRAL NERVOUS SYSTEM DISORDERS

Olsztyn, October 24, 2014
11:00 Opening of the symposium

Session I – Chair: Prof. dr hab. n. med. Wojciech Maksymowicz (Department of Neurology and Neurosurgery, Faculty of Medical Sciences, University of Warmia and Mazury in Olsztyn)

11:10 ~ 11:50 Prof. Adam Czapliński (Department of Neurology and Neurosurgery, Faculty of Medical Sciences, University of Warmia and Mazury in Olsztyn; Neurology, Neurozentrum Bellevue, Zurich, Switzerland)

"Stem cells: new hope for treating ALS?"

11:50 ~ 12:30 Prof. dr hab. n. med Krzysztof Selmaj, dr Mariola Matysiak (Department of Neurology, Medical University of Łódź)

"Mesenchymal stem cells in multiple sclerosis treatment."

12:30 ~ 13:10 Prof. Jeff W. M. Bulte (Cellular Imaging Section, Institute for Cell Engineering Johns Hopkins Baltimore)

"MRI Tracking of Stem Cells in Neurodegenerative Disorders"

13:10 ~ 13:50 Lunch

Session II – Chair: Prof. dr hab. n. med Krystyna Domanska-Janik (Chairman of Cell Therapy Team of The Central Nervous System Diseases (CTT-CNS) Polish Academy of Sciences)

13:50 ~ 14:30 Prof. Alexander Storch (Division of Neurodegenerative Diseases, Technische Universität Dresden)

"Stem-cell based treatment approaches in neurodegenerative disorders."

14:30 ~ 15:10 Prof. Yang D. Teng (Departments of Neurosurgery and Physical Medicine & Rehabilitation, Harvard Medical School)

"Recovery Neurobiology of SCI: Insight Gleaned from Functional Multipotency of Stem Cells"

15:10 ~ 15:40 Prof. Bogusław Machaliński (Department of General Pathology, Pomeranian Medical University in Szczecin)

"The role of paracrine effects in adjuvant stem cell-based therapies of neurodegenerative disorders"

15:40 ~ 16:00 Coffee Break

16:00 ~ 16:40 Prof. Marcin Majka (Department of Clinical Immunology and Transplantology, Collegium Medicum of the Jagiellonian University)

"Is it possible to treat Parkinson's Disease with pluripotent stem cells? Pros and cons"

16:40 ~ 17:10 Dr Anna Sarnowska (NeuroRepair Department, IMDiK PAN, Warsaw)

"Tissue-derived stem cells: what must be done before clinical transplantation"

17:10 ~ Closing remarks
LIST OF ABSTRACTS

Session I – Chair: Prof. dr hab. n. med. Wojciech Maksymowicz

1.1 Prof. Adam Czapliński - „Stem cells: new hope for treating ALS?”

1.2 Prof. Krzysztof Selmaj, dr Mariola Matysiak - „Mesenchymal stem cells in multiple sclerosis treatment.”

1.3 Prof. Jeff W. M. Bulte - “MRI Tracking of Stem Cells in Neurodegenerative Disorders.”

Session II – Chair: Prof. dr hab. n. med Krystyna Domanska-Janik

2.1 Prof. Alexander Storch - “Stem-cell based treatment approaches in neurodegenerative disorders.”

2.2 Prof. Yang D. Teng - “Recovery Neurobiology of SCI: Insight Gleaned from Functional Multipotency of Stem Cells.”

2.3 Prof. Bogusław Machaliński - “The role of paracrine effects in adjuvant stem cell-based therapies of neurodegenerative disorders”

2.4 Prof. Marcin Majka - “Is it possible to treat Parkinson’s Disease with pluripotent stem cells? Pros and cons”

2.5 Dr Anna Sarnowska - “Tissue-derived stem cells: what must be done before clinical transplantation.”
1.1 Stem cells: new hope for treating ALS?

Adam Czapliński

Department of Neurology and Neurosurgery,
Faculty of Medical Sciences,
University of Warmia and Mazury in Olsztyn
Neurology Neurozentrum Bellevue, Zurich, Switzerland

In recent years, considerable effort has been made to improve the treatment of patients with amyotrophic lateral sclerosis. Therapy with riluzole has been proved to increase survival in controlled trials. Moreover, the introduction of percutaneous gastrostomy (PEG) and non-invasive ventilation (NIV) has been shown to prolong survival and improve quality of life. However, there is still no cure for the ALS. Any experimental therapeutic approach to ALS is very difficult because of some peculiarities of the disease, such as the unknown origin, the spatial diffusion of motor neuron loss and the paucity of animal models. Despite such daunting challenges, in experimental models a number of potential benefits of stem cells in ALS therapy have been demonstrated: by providing non-compromised supporting cells such as astrocytes, microglia or growth factor-excreting cells, onset can be delayed and survival increased. Moreover, in animal models of acute or chronic motor neuron injury, neural stem cells implanted into the spinal cord have been shown to differentiate into motor neurons, with some evidence of axonal sprouting and formation of neuromuscular junctions with host muscle.

In his talk, Prof Czapinski will focus on clinical aspects of stem-cells transplant and give an overview about recent stem-cell trials in ALS. He will also present first preliminary data of a current phase I clinical trial performed in Olsztyn.
Multiple sclerosis (MS) is a progressive inflammatory neurodegenerative disease of the central nervous system (CNS) that is characterized by inflammation, demyelination and damage of neurons and axons. Current therapeutic intervention predominantly modulate the immune system but have non or little effect on the neurodegenerative component of the disease. About ten years ago the first data have shown that intravenous transplantation of mesenchymal stem cells (MSC) ameliorates experimental autoimmune encephalomyelitis (EAE), an animal model of MS. The immunomodulatory, tissue protective and regenerative properties of MSC make them an attractive potential therapy for MS patients. The overall published experience with MSC treatment of MS revealed clinical effectiveness and very promising safety profile, therapy was well tolerated. The current aim in the development of MSC-based strategies for the treatment of MS is to have treatment potential demonstration in large clinical trials. The better understanding of immunomodulatory and neuroprotective properties of MSC in MS patients is of great importance for future development of cell-based therapy in this disease. Ten years experiences in field of MSC therapy of EAE and MS gave answers to many questions, but even more questions still remain unanswered.
1.3 Tissue-derived stem cells: what must be done before clinical transplantation

Jeff W.M. Bulte, M. Janowski, P. Walczak

Russell H. Morgan Dept. of Radiology and Radiological Science, Division of MR Research, Cellular Imaging Section and Vascular Biology Program, Institute for Cell Engineering, The Johns Hopkins University School of Medicine, Baltimore, MD, USA.
jwmbulte@mri.jhu.edu

Translational cellular imaging is expected to play a key role in evaluating the outcome of clinical trials in regenerative medicine that are using stem cells. In order to facilitate and implement the translation of novel therapies into the clinic, it will be necessary to monitor immediate cellular engraftment, subsequent biodistribution and migration, and cell survival and differentiation non-invasively over time. MRI cell tracking, with its superior spatial resolution and excellent soft tissue anatomical detail, is emerging as the technique of choice to monitor in real-time image-guided cell delivery and engraftment. Up until now, 9 clinical MRI cell tracking studies have been published, all using superparamagnetic iron oxide nanoparticles or SPIOs in an off-label fashion. SPIOs create strong local magnetic field disturbances that spoil the MR signal leading to hypo- or hyperintense contrast.

Another approach is to fluorinate stem cells and follow them using “hot spot” 19F MRI. At least 2 clinical trials have been registered. An emerging field, although not yet clinical, is the development of MRI reporter genes, e.g. ferritin, lysin-rich protein, supercharged GFP, and thymidine kinase, to name a few. Unlike labelling with SPIO or fluorine, these proteins enable the determination of cell survival and differentiation, when the reporter is placed under a specific promotor. In addition, the allow tracking of rapidly dividing cells, as the genetic material is replicated unlike the chemical labels. We will provide an overview of available MRI cell tracking techniques, and show specific examples of real-time targeted intra-arterial delivery, the clinical surprises, and the latest pre-clinical reporter gene studies.

Recommended further reading

2.1 Stem-cell based treatment approaches in neurodegenerative disorders

Takahashi and Yamanaka pioneered the field of somatic cell reprogramming by identifying four transcription factors which are – when overexpressed in a somatic cell – sufficient to induce a cell harboring all properties of a pluripotent stem cell. The so-called induced pluripotent stem cells (iPSCs) are thus able to be differentiated in all cell types of the body. This technology is a tremendous breakthrough in medical science since any cell type can now be derived patient-specific with the potential for autologous cell replacement strategies and personalized medicine. However, further advances in direct lineage conversion of somatic cells into neurons (induced neurons; iNs) or expandable multipotent neural stem cells (induced neural stem cells; iNSCs) provides interesting alternatives to the iPSC technology to generate neurons or other neural cell populations for both cell replacement and disease modelling for neurodegenerative diseases.

iPSCs perform like embryonic stem cells (ESCs) during cell type differentiation, therefore most protocols already established for ES cell differentiation are – in general – applicable for iPSCs. Exemplarily, dopaminergic differentiation from Parkinson's disease (PD) patient-derived iPSCs was proven in vitro and in vivo by restoration of hemiparkinsonian rats after intrastriatal transplantation. Within this gold rush mood of the recent iPSC years, large parts of the scientific and clinical community neglect some major problems accompanied with the use of pluripotent stem cells such as their tumorigenicity. Moreover, there are unclear limitations with the use of iPSCs in clinical application such as their genetic and epigenetic instability and heterogeneity.

Another potential application of iPSC as well as the directly induced somatic counterparts such as iNs and iNSCs is their use as in vitro cell model systems for various neurodegenerative diseases and iPSCs are hoped to catalyze our understanding in neurodegenerative diseases. However, one major obstacle is whether it will be possible to model neurodegenerative disorders as age-dependent diseases since cellular reprogramming reprogram the cell to an embryonic stem cell state. Nevertheless, first reports promisingly show neuronal cell degeneration in various iPSC-based disease models, e.g. spinal muscular atrophy or PD.

The presentation does not only provide a comprehensive overview of the different cellular candidates including their assets and drawbacks with their use as model systems for neurodegenerative diseases, but also of the various additional issues that need to be addressed in order to convert cellular replacement therapies from an experimental to a clinically relevant therapeutic alternative in neurodegenerative diseases.

Funding: Research of the author was supported by the Bundesministerium für Bildung und Forschung, the Deutsche Forschungsgemeinschaft (DFG) through the Sonderforschungsbereich 655 “From cells to tissues”, the DFG-Research Center and Cluster of Excellence “Center for Regenerative Therapies Dresden (CRTD)”, the German Center for Neurodegenerative Diseases (DZNE), the Thyssen-Stiftung, the Landesstiftung Baden-Württemberg and the Helmholtz Association through the Virtual Institute “RNA dysmetabolism in ALS and FTD”.

Alexander Storch
Division for Neurodegenerative Diseases, Department of Neurology, Technische Universität Dresden, 01307 Dresden, Germany
German Centre for Neurodegenerative Diseases (DZNE) Dresden, 01307 Dresden, Germany
Center for Regenerative Therapies Dresden (CRTD), Technische Universität Dresden, 01307 Dresden, Germany
2.2 Recovery Neurobiology of SCI: Insight Gleaned from Functional Multipotency of Stem Cells

Prof. Yang (Ted) D. Teng, Ph.D., M.D.

Departments of Neurosurgery and Physical Medicine & Rehabilitation (PM&R)
Harvard Medical School and Veterans Affairs Boston Healthcare System, Boston, MA, USA

Emerging evidence increasingly suggests that stem cells may help repair the central nervous system through multiple mechanistic strategies that are often concurrent (i.e., functional multipotency). They may serve not only as tissue engineering mediators of cellular reconstitution, but also as vectors for the delivery of molecules. Based on results derived from our recent studies in which biodegradable polymer seeded with human neural stem cells (hNSCs) or human mesenchymal stromal stem cells (hMSCs) was applied for both investigative and therapeutic purposes, I will first discuss that how tailored polymer implants containing hNSCs or hMSCs may hold significant promise for providing a broad range of insight regarding essential neurological mechanisms required for repairing the adult mammalian spinal cord after injury. I will present data elucidating cellular and molecular events underlying secondary loss of host and donor cells in acutely injured spinal cord and counteracting strategies proved effective in a rat model of penetrating spinal cord injury (SCI) using a retrievable design of PLGA scaffolded hNSCs that were shielded by drug-releasing polymer. Additionally, data obtained by investigating functional multipotency of hNSCs and hMSCs plus genetic reduction of reactive gliosis or peripheral nerve anastomosis will be analyzed for understanding the role of distal spinal cord plasticity in defining recovery neurobiology post SCI and non-cell autonomous pathogenesis of motor neuron diseases. Our findings may provide a stem cell-based multimodal approach to investigating and formulating therapeutic strategies to achieve clinically meaningful improvement for SCI and neurodegenerative diseases.
2.3 Is it possible to treat Parkinson's Disease with pluripotent stem cells? Pros and cons

Marcin Majka

Department of Transplantation Jagiellonian University Collegium Medicum,
265 Wielicka Str., 30-663, Cracow, Poland

In a rapidly aging population, neurodegenerative diseases affect growing number of people. Unfortunately, for the majority of patients there is no efficient treatment available today. That is also the case with Parkinson's Disease (PD) patients. This age-dependent disorder, characterized by motion problems still remains the incurable disease. However, basing on the latest advances in the field of stem cell research and development of induced pluripotent stem (iPS) cells, we might be facing the new opening in the treatment of PD.

Recently, several papers were published showing that iPS could be differentiated toward dopaminergic neurons and improve the PD symptoms in animal models. IPS cells were also used to model the PD through a genome editing and incorporation of PD related mutations. These discoveries open new avenues for developing efficient treatment. Also the latest publication describing positive long-term outcome of PD patients transplanted with fetal brain tissue brings the hope for patients.

However, the safety of using pluripotent stem cell still remains an issue. The major problem that keeps us from using these cells in a clinic is their ability to form teratomas. Thus, development of new strategies intended to eliminate the risk of tumor formation are necessary.

Despite that problems, it is very likely that the newest accomplishments in the stem cells field will bring new treatment modalities for patients with Parkinson's disease and other neurodegenerative diseases.
2.4 The role of paracrine effects in adjuvant stem cell-based therapies of neurodegenerative disorders

Bogusław Machaliński

Department of General Pathology,
Pomeranian Medical University, Szczecin, Poland

Recently, increased emphasis arose on novel treatment for neurodegenerative disorders using stem cell-based therapies, which have been widely investigated in two major directions: cell replacement and trophic support. The first approach aims at replacing the degenerated neurons, while the latter claims that stem/progenitor cells might provide a neuroprotective microenvironment for damaged tissue and save the remaining neurons. Although there is currently lack of compelling evidence for the effectiveness of cell-replacement therapies, the list of cells that are under investigation is relatively long and includes embryonic SCs, immortalized cell lines, and BM- and UCB-derived SPCs (e.g., MSCs). Many factors might influence the efficacy and safety of cell transplantation in neurodegenerative disorders; these factors include the type and number of cell populations to be transplanted, the site and timing of the cell application, age, morbidity status of the patient, etc. As the main benefit that is accessible from transplanted cells, paracrine secretory activity is theoretically the most convincing and fits nicely into the concept of adjuvant/supportive roles for SC-based therapy. In recent years, numerous studies have shown that stem cell transplantation elicits neurogenesis and angiogenesis by releasing neuroprotective factors, including neurotrophins, which regulate the growth, differentiation, and migration of neural stem/progenitor cells (SPCs). Based on our findings, we suggest that transplantation of SPCs provides neuroprotective effects by production of cytokines/growth factors and may delay disease progression.
2.5 Tissue-derived stem cells: What must be done before clinical transplantation

Anna Sarnowska,
Katarzyna Drela,
Patrycja Siedlecka,
Krystyna Domańska-Janik

NeuroRepair Department, Mossakowski Medical Research Centre,
Polish Academy of Sciences, 5 Pawinskiego Street, 02-106 Warsaw,

For last few years we can observe increasing number of ongoing clinical trials with stem cells application. The most commonly used in a clinic are human mesenchymal stem cells. Their regenerative action is thought to be evoked by strong immunomodulatory as well as cell replacement capabilities. Unfortunately among conducted trials substantial differences in treatment protocols and stem cell derivation/cultivation procedures unable positive falsification of the results scattered from the lack of effects to the full recuperation.

Searching for the reasons of divergence in neuroprotection induced by MSC treatment we have focused on the interrelation between environment, phenotypic cell evolution depending from culture conditions and interactions between “therapeutic” WJ-MSC cells and targeted tissue. For this we used the co-culture model of human WJ MSC with intact or injured by oxygen glucose deprivation (OGD) rat organotypic hippocampal slices.

Our experiments showed that the strongest ability for neuroprotection was provided by freshly excised pieces of WJ tissue and the first cohort of migrating MSC cells (passage O). Along further passaging the cells phenotype changed substantially and cell neuroprotective effect declined together with modification of paracrine capabilities of WJ-MSC-secreted cytokines.

These results will be challenged with our previous data gathered in preclinical and clinical experimentations showing that undifferentiated, SRTF* expressing MSC, capable to time-locked proliferation, migration and ultimately to neural differentiation are the most effective in various therapeutic transplantation models.