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Review of the First Fraunhofer Life Science Symposium on Cell Therapy and Immunology - October 22-24, 2006, Leipzig, Germany

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Abstract: This report covers recent advances in Regenerative Medicine with a special focus on (i) imaging of regeneration, (ii) nanotechnology and tissue engineering, (iii) immunological cell tolerance, (iv) cell therapies in cardiovascular, neurodegenerative, and liver diseases and in spinal regeneration.

Introduction

Regenerative Medicine focuses on developing therapies that reestablish tissue and organ function impaired by trauma or disease. Advances in the development of bioengineered cells and the transplantation of differentiated cell types as well as stem cells offer new possibilities for tissue regeneration. In 2007 research centers for Regenerative Medicine have been founded at different Universities, including Berlin, Dresden and Leipzig, illustrating the high interest in implementation of new technologies for treatment of complete or partial loss of tissue or organ function. Progress in cell therapy depends on the availability of adequate cell types and transplantation protocols for specific tissues, tolerance to transplanted cells and on reliable imaging techniques. Therefore, innovative techniques in cytometry, positron emission tomography (PET) and magnetic resonance (MR) imaging as well as cell tagging by fluorescence markers represented one of the three main topics of this meeting. A second focus was transplantation tolerance defined as a state of specific immunologic unresponsiveness to foreign antigens of a graft in the absence of maintenance immunosuppression. A third highlight was state of the art presentations and innovative concepts of cell therapies for specific tissues, namely the heart, brain, liver and bone.

Imaging of regeneration

This session began with a report given by **Attila Tarnok** (Leipzig Heart Center) from the 16th Annual Meeting of the German Society of Cytometry (DGfZ, www.dgfz.org) which took place in Leipzig a few days before the Fraunhofer Life Science Symposium. Attila Tarnok who is currently president of the DGfZ summarized the highlights of the DGfZ meeting, which are in most cases related to new techniques for in vivo and high-content fluorescence imaging, under the catchword "Cytomics emerging from Cytometry". Main topics discussed in this context were the question whether these techniques will in future find their way into human applications, and whether small animal optical imaging will be possible in a tomographic approach. Here, both questions were answered positively. One example for

human applications represents the intra-operative search for putative tumor residuals after local tumor resection.

Secondly, **Henryk Barthel** (Department of Nuclear Medicine, University Leipzig) gave an overview regarding the current state of "PET imaging of regenerative therapies" as well as insight into future developments in this regard. Major strengths of PET as a sensitive in-vivo imaging approach are seen in (i) early and accurate detection of tissue degeneration, (ii) visualization of stem and immune cell action by direct cell labeling and (iii) non-invasive monitoring of therapy response. For diagnosis of degeneration tissues, direct (such as blood flow in stroke or ß-amyloid in Alzheimer's disease) and surrogate (like hypoxia in stroke or dopamine transporters in Parkinson's disease) parameters are visualized and quantified by PET. One exciting new development is related to imaging devices which combine the functional-oriented macroscopic PET technique with anatomical (PET-CT, PET-MRI) or microscopic (PET-Fluorescence) imaging approaches.

Next, **Jeff Bulte** (The Johns Hopkins University School of Medicine, Baltimore, USA) reported on "MR imaging of stem cells and immunotherapy". Prof. Bulte is world-wide one of the leading experts in this fast-developing imaging field. His research is directed towards new techniques to reliably label stem and immune cells with iron oxide particles through the use of magnetoelectroporation. The major advantage of MR for cell imaging is its high spatial and temporal resolution which allows for accurate control of the correct localization of the stem cell placement in case of local injection, and for fast dynamic studies of stem cell distribution/homing in case of systemic applications.

Finally, in a Special Lecture, **Oliver Hayden** (IBM Research, Zurich, Switzerland) gave fascinating insights into the world of "Low-dimensional materials for life science applications": Main examples given in this talk where the use of quantum dots (QDs) and superparamagnetism. QDs are fluorescent semiconductor nano-crystals with different layers which can be functionalized (for instance with antibodies or receptor ligands) for specific applications like immune cell tagging. Apart from this feature, high stability and the lack of relevant bleaching are mayor advantages of QDs, which stand against possible drawbacks in translating this technique into human use due to toxicity matters. The phenomenon of superparamagnetism is currently under application to treat advanced human brain tumors. For that purpose, magnetic fluids are administered which accumulate within the tumors. After applying a magnetic field, a hyperthermia is induced with the aim to reduce the tumor load. Oliver Hayden reported on promising preliminary results obtained in an according clinical study which is currently under way at the Charité University Hospital Berlin (Germany).

Immunology

The first session dealt with the somewhat neglected topic in the area of advanced therapy products regarding the immunogenicity of allogeneic and xenogeneic cell therapies. Particularly interesting in this meeting was the opportunity for high-level immunologists active in tolerance research to exchange information with top cell therapy researchers in neuroscience, cardiovascular research and hepatology.

Frank Emmrich (Fraunhofer Institute for Cell Therapy and Immunology, Leipzig) introduced the topic with a few words outlining our current understanding of tolerance through the odyssey of the Waldmann group in London whose quest to understand tolerance lead them to postulate "T-suppressor cells" that could mediate tolerance. The struggle to characterize and prove the existence of such cells finally came to fruition in 2003 with the characterization of "T-regulatory" cells that are now known to actively support tolerance through

mediation of several aspects of the immune response. We also now understand that antibody mediated tolerance can furthermore be induced through co-stimulatory blockade by antibodies which block specific signals between the antigen presenting cells and T-suppressor cells.

Further expanding on the regulation of T-regs, **Kathryn Wood** (University of Oxford, London) reminded the audience that a balance exists between the innate and adaptive immune responses. Through the work of several other groups including those mentioned by Frank Emmrich, it is now understood that T-regs are CD4+, CD25+, Tr1 and Th3 positive cells that naturally occur and are induced in response to antigens. Furthermore, it appears that the natural T-reg response is inhibited by immunosuppressant calcineurin inhibitors (CNIs), and many physicians are therefore sparing CNIs in the first days after organ transplant to encourage this response.

In the unpublished results of Kathryn Wood they demonstrated that sirolimus plus antigen exposure results in the stimulation of T-regs that are CD25+, CD4+, FoxP3+ and could regulate responding T-cells, aggressive T-cells and B-cells. This was shown to occur through IL10, CD152 and TGF-beta. Their new data also shows that donor derived dendritic cells co-cultured with recipient T-cells with a low dose of IFN-gamma in the culture results in T-cells (no IL4) that enrich FoxP3+ cells. Thus IFN-gamma conditioned cells can prevent skin and islet rejection, and tolerance to alloantigens cannot be induced without INF-gamma. The implications of these results are that in order to encourage and/or induce natural tolerance mechanisms in organ transplant patients, changes in immunosuppressive regimes (phasing out of CNIs, or late introduction) may be necessary and expedient.

Bernd Arnold (German Cancer Research Center, Heidelberg) introduced the idea that tolerance could also be mediated by CD8+ cells and not only CD4+ cells. His talk focused on peripheral T-cell tolerance in the developing immune system as opposed to the adult immune system. When the immune system is being constructed in the young animal, the neonate faces an immune deficient environment in the periphery – naïve T-cells must migrate into non-lymphoid tissues that are lymphopenic. This talk focussed on how this condition is regulated in order to shed light on how to induce tolerance in the adult animal. Arnold demonstrated that the mechanisms governing this process are T-cell independent.

In neonates, T-cell expansion is dependant on IL-7 (as shown by knock-out experiments). As Jak3 is also in the IL-7 pathway, Jak3 knockouts have a similar phenotype. In neonates up to 2 weeks old, a non-T-cell, which remains undiscovered, regulates homeostasis in a IL-7 dependent fashion. Additionally, a CD11b myeloid suppressor cell keeps the number of memory T-cells down. T-cell migration in the neonate into tissues triggers self-tolerance.

Experiments using a skin-specific antigen activated tolerance, inducing long-lasting CD8+ cells. Finally, failure to limit CD8+ cells leads to autoreactivity. In conclusion, non-T-cells balance tolerant CD8+ T-cells and prevent graft rejection by naïve T-cells with the same receptor. Also, regulatory CD8+ T-cells can induce tolerance and active T-cells may prevent tissue destruction.

Shifting gears somewhat, **Yair Reisner** (Weizmann Institute of Science, Israel) and **Tomo Saric** (Institute for Neurophysiology, University of Cologne) spoke regarding the immunogenicity of embryonic stem cells, a hot topic as many are looking into the applicability of these cells.

Tomo Saric tackled the questions surrounding the immunological properties of murine embryonic stem cells and the immunologic status of these cells following differentiation. Although ES cells and their derivatives were demonstrated to express

low levels of MHC molecules making them detectable by the immune system in theory, undifferentiated ES cells are in actuality curiously resistant to killing by cytotoxic T-cells. This protection is shown to persist also as ES cells further differentiate into embryoid bodies. This information is critical for those interested in using ES cells for allogeneic therapies. However, it still remains to be shown if rejection may become a concern after cells derived from ES cells are transplanted.

Although many groups would like to use human embryonic stem cells in stem cell therapy, Yair Reisner pointed out that there is utility point between growth potential, tumorigenicity, and immunogenicity that needs to be balanced.

Currently, embryonic stem cells cause teratomas when used for therapy.

Yair Reisners group has discovered astoundingly, that if the pig embryonic pancreas precursor cells are used after embryonic day 28 (E28), there is no risk of a teratoma following transplantation into diabetic SCID mice. They found that in pig embryos there is a window, between 4 weeks, when no teratoma forms, and 6 weeks when cells become immunogenic, and are rejected that represents the optimal use of foetal cells. The corresponding window with human foetal tissues has also been tested in Prof. Reisners lab and was found to be between 7-8 weeks.

Furthermore, Yair Reisners group has also found that different tissues have different optimal windows of use. For example, porcine embryonic pancreas progenitor cells taken at E42 were shown to be ideal for transplantation, and data regarding ideal time-points for cell therapy for liver and lung was also presented. The group also confirmed that there are no APCs in transplanted porcine foetal tissues before E42. Finally, in a group of very interesting experiments the Reisner group found that one can use co-stimulatory blockade with E42 pancreatic stem cells to achieve tissue acceptance in xenogeneic (pig to mouse) tissue therapy with no teratoma. The reason that many previous experiments have failed with islets transplantations is likely that they were far outside of the optimal window.

Cell Therapy of the Liver

The progress made in the field of liver organ transplantation has revolutionised the treatment of a wide spectrum of liver diseases. Nevertheless, cell-based therapies are emerging as an alternative to whole organ transplantation. Hepatocyte transplantation has been used to bridge patients to whole organ transplantation to decrease mortality in acute liver failure. **Etienne Sokal** (Cliniques Universitaires St. Luc, Dept. of Pediatric Hepatology and Liver transplantation, Brussels, Belgium) presented several examples where hepatocyte transplantation has improved metabolic liver disease. For instance, successful hepatocyte transplantation has been achieved in a 4 year old girl with infantile Refsum disease, an inborn error of peroxysome metabolism, leading to increased levels of serum bile acids and the formation of abnormal bile acids. A total of 2×10^9 hepatocytes from a male donor were given during eight separate intraportal infusions. Abnormal bile acid production had decreased by 40 % after 18 months. Abnormal bile acids disappeared form the serum, in parallel with the reduction of cholestasis (total bile acids), pipecholic acid (- 40%) and very long chain fatty acids. Another very successful patient with urea cycle disorder (argino succinate lysase deficiency) was reported. The child received repeated infusion of fresh and cryopreserved liver cells leading to full control of hyperammoniemia and neurological improvement. Engrafted cells and tissue enzyme activity were detected in the recipient liver tissue up to one year after liver cell transplantation. Other clinical successes were reported in type I glycogenosis and Crigler Najjar patients. A limitation of long-term success is rejection of the transplanted allogeneic hepatocytes.

Therefore, improvement of immunosuppression is crucial. Cell transplantation is less invasive than whole-organ transplantation and can be performed repeatedly. However, one major limitation of cell-based therapies for liver disease is the availability of human hepatocytes. A wider use of these techniques will not be possible until adequate numbers of functional cells for transplantation become more readily available. Therefore, three speakers, **Andreas Nüssler** (Fresenius Biotech Bad Homburg, Div. of Cell Therapy and Charite, Berlin) **Michael Ott** (Medizinische Hochschule Hanover, Dept. of Gastroenterology, Hanover Germany) and **Jan G. Hengstler** (Center for Toxicology, University of Leipzig, Germany) presented results about the use of stem and precursor cells in therapy of liver diseases. In recent years, numerous articles have reported about the generation of liver cells or 'hepatocyte-like cells' from different types of extrahepatic stem or precursor cells. At first glance, this appears to provide exciting new opportunities for cell therapy, as some types of stem cells proliferate efficiently *in vitro* and therefore may help to generate a larger supply of human hepatocytes or precursor cells for transplantation. Without doubt, the wide availability of human hepatocytes would be considered a major breakthrough and may open new perspectives for the treatment of liver disease. On the other hand, some studies presenting with far - reaching conclusions with respect to the capacity of stem cell therapy have not yet been reproduced or may have been interpreted in an over-optimistic manner. Andreas Nüssler gave an overview about monocyte-derived hepatocyte-like cells (NeoHep cells) and carefully compared this cell type to primary human hepatocytes. NeoHep cells are obtained from human blood monocytes using a two-step dedifferentiation/ differentiation protocol. These cells express some (e.g. urea synthesis, phase II metabolism) but not all hepatocellular functions. For clinical application an advantage of the monocyte derived hepatocyte-like cells would be the opportunity to generate these cells from the recipients own blood, thus avoiding immune suppressive medication. Michael Ott compared embryonic and somatic (haematopoietic) stem cells for their differentiation capacity. Haematopoietic stem cells did not form real hepatocytes after transplantation into mice. In contrast, embryonic stem cells could be differentiated into the hepatic lineage, suggesting a superiority of this cell type. Of course, a possible tumorigenicity must be carefully evaluated. Jan G. Hengstler presented data after transplantation of extrahepatic stem cells (from cord blood, bone marrow, monocytes and pancreas) into livers of NOD/SCID mice combining tracking techniques and marker analysis in the same cells. A complex situation was observed suggesting only partial differentiation and horizontal gene transfer between the transplanted cells and the host's hepatocytes. Although stem cell based treatment of liver diseases is an attractive strategy, these approaches are conceptual and still far from clinical application.

Cell Therapy: Neurology

Treatment of degenerative processes and acute, traumatic or ischemic damage of the central nervous system (CNS) is of high relevance because these diseases lead to a substantial lost of function in many brain systems. However, there has been a noticeable progress in developing new therapeutic strategies aiming at diseases of this most complex organ. **Karoly Nikolich** from the Neuroscience Institute at Stanford (Stanford University Medical School, Stanford, California, USA) reviewed principle mechanisms of new therapies for the injured CNS and summarized current challenges. Because neuronal plasticity is often blocked by inhibitory processes and/or glial scar formation and neuronal differentiation of endogenous or delivered stem cells is not crucial for functional improvement, the talk focused on the potential of pharmaceutical interventions. Actually, a broad variety of antibodies, growth factors and small

molecules is evaluated in a preclinical stage or has even reached clinical trials. **Stefan Krauss**, at the Norwegian Stem Cell Center (National Hospital and University of Oslo, Oslo, Norway), presented novel data concerning the role of canonical Wnt signalling in stem cell maturation, especially in the cortex and the hippocampus. Using conditional knock out mice, Stefan Krauss´ group was able to identify processes going on from day E10 to E14 altering the genetic program of cortical neural stem cells. These mechanisms induce a transcription program that causes stem cells giving rise to radial glia first and then triggers neuronal differentiation. Understanding the processes of development and formation of neuronal circuits might lead to new approaches for neural replacement and integration based on the use of stem cells upon brain injury. The role neural stem cells and dopaminergic precursors in the potential treatment of Parkinson´s disease (PD) was reviewed by **Johannes Schwarz** from the University of Leipzig (Leipzig, Germany). Parkinson's disease is a chronic, progressive neuro-degenerative movement disorder characterized by a continuous and rather selective loss of dopaminergic neurons in the substantia nigra pars compacta with subsequent striatal dopamine depletion. Consequently, transplantation of neural stem cells that were expanded in vitro and forced to dopaminergic differentiation showed an encouraging capacity of causing functional improvement in animal models of PD. The grafts survived and integrated in the host brain. However, first clinical trials using primary embryonic tissue for transplantation of PD patients initiated in the late 80ies and early 90ies showed significant variability in respect to their primary endpoint and functional outcome. The prospect of using neural precursor cells that are well described and enriched for dopamineric precursors will dramatically change the possibilities of restorative therapy in this disorder. Thus, PD may be the first neurodegenerative disorder in which clinical application of stem cell derived tissue might become true.

Alternatives to Human Embryonic Stem Cells

A special lecture was given by **Gerd Hasenfuss** from the Department of Cardiology and Pneumology, Heart Center, Georg-August-University of Göttingen (Göttingen, Germany) who first identified pluripotent spermatogonial cells in the adult mouse testis that may be an alternative to embryonic stem (ES) cells. The use of embryonic stem cells is limited by small availability and ethical considerations. Based on findings that embryonic germ cells as well as germline cells from neonatal rodent testis are pluripotent, Hasenfuss isolated adult spermatogonial cells which are responsible for maintaining of spermato-genesis throughout the lifespan of a male individual. When transferred to a blastocyst, these cells contribute to the generation of a variety of organs including heart, brain, liver and kidney. After cultivation of those cells in hanging drops, the group was able to show an impressive differentiation potential of the isolated cells in vitro giving rise to the most important cell types of organ systems derived from all three blastodermic layers.

However, the preclinical and clinical use of these cells is still restricted by the potential danger of teratoma formation upon cell transplantation in living beings. Prevention of this danger by efficient pre-differentiation and selection strategies will be of crucial relevance before transferring therapeutic approaches of ES and ES-like cells into the clinic, as reported by Gerd Hasenfuss.

Cell Therapy – Spinal Cord

This section dealt with difficulty of axonal regeneration as well as the problem of disc repair. **Jürgen Borlak** (Fraunhofer ITEM Hannover) started off the session with a presentation regarding the usefulness of BENZ compounds in promoting axon outgrowth. BENZ compounds are myelin-associated-glycoprotein (MAG) / siglic-4 inhibitors that promote neurite outgrowth in vitro. The magnitude of neurite outgrowth

can be quantitated, and such experiments demonstrate that these compounds lead to increased neuronal survival as well as inhibition of MAG expressing cells. In gene chip analysis of DRG (dorsal root ganglion) cultures BENZ compounds have also been shown to up-regulate neuroprotective genes. There is a clear potential use for BENZ compounds in spinal cord injury.

The next talk by **Koichi Masuda** (Rush University Medical Center, Chicago) focussed on disc repair through therapeutic injection of growth factors BMP-7 or rhGDF-5 directly into damaged spinal discs. This group has convincingly shown improvement through MRI following treatment, and will be following up with clinical trials. Furthermore, the rabbit puncture model showcased here for these experiments has also been used by the lab to test the utility of BMP-7 incubated stem cell therapy in repair of spinal discs, these experiments are ongoing.

Continuing on with the subject of degenerative disc disease, **Hans Jörg Meisel** (BG Clinic Bergmannstrost, Halle) presented the interim results of a randomized multi-center clinical trial carried out in conjunction with EURODISC, in which autologous cultured disc derived chondrocytes (ADCT) were administered to patients suffering from degenerative disc disease. Control patients were treated with the conventional discotomy and the experimental group with discotomy plus cells. A significant improvement was demonstrated in the ADCT treated patients.

Returning to the subject of axonal repair, **Eva Syková** (Academy of Sciences and Charles University, Prague) presented results from several avenues of inquiry regarding cell therapy for spinal cord injury. In one group of experiments with a balloon-induced rat spinal cord compression lesion model, mesenchymal stem cells used to treat injury resulted in migration of cells to the injured site, but as other groups have demonstrated, very little differentiation into neurons (3%) despite improvement in outcomes. MSCs here appear to serve as delivery vehicles for grown factors. This model has been translated into a pilot clinical trial in which 27 patients were treated with autologous BM derived mononuclear stem cells, (i.v or closer to the injury site) there were documented signs of improvement even in patients that had been injured up to 4 weeks after the injury. In further experiments using a different rat model, adult or embryonic stem cells seeded onto biodegradable hydrogel (HEMA) nano-fibre scaffolds were used to bridge the gaps. Neuronal cells infiltrate the scaffold but astrocytes do not. Stem cell treated animals displayed more rapid recovery.

Cell Therapy: Cardiovascular

Stem Cells and Cardiac Repair

For many decades, the heart was considered to be a postmitotic organ. This dogma conceptually excluded the replacement of damaged myocardium and implied that an individual must manage the entire life with the number of cardiomyocytes that are present at birth. This view has been challenged by **Piero Anversa** (New York Medical College) and co-workers, who demonstrated the existence of a population of primitive cells within the mammalian heart that posses the ability to regenerate. These cardiac progenitor cells isolated from the heart of different animals were shown to be self-renewing, clonogenic and multipotent in vivo and in vitro thereby contributing to the formation of functional myocardium. However, it was not known whether a similar population of stem cells exists in the human heart. In his talk, Piero Anversa presented preliminary data suggesting that a similar population of primitive cells may be present in the human heart as well.

Current Status of Clinical Trials in Cardiology

From the clinical point of view, the prognosis of patients following acute myocardial infarction is mainly determined by the degree of left ventricular remodelling.

In order to prevent deleterious alterations of the left ventricle after myocardial infarction, the regenerative potential of bone marrow-derived and circulating progenitor cells was first evaluated in animals studies, which showed an attenuation of left-ventricular remodelling, an improvement in cardiac function and myocardial perfusion as a result of stem cell application. These beneficial effects inspired researchers to conduct clinical trials, which were presented by **Axel Linke** (Heart Center Leipzig Gmbh). In a pilot study, published by Strauer and co-workers in 2002, intracoronary infusion of BM-derived stem cells was shown to reduce infarct size and consequently increase myocardial perfusion at three months follow-up. In the TOPCARE-AMI-trial (Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction), the therapeutic effects of circulating progenitor cells and bone-marrow stem cells were assessed in patients with acute MI. Also in this study, application of both cell types resulted in a comparable and significant improvement of ejection fraction at 4 months follow-up. Interestingly, a further gain in left ventricular performance was observed between 4 and 12 months of follow-up. The BOOST (BOne marrOw transfer to enhance ST-elevation infarct regeneration) trial, which was the first study using a controlled design confirmed these results. In contrast to many studies showing positive effects, the trial published by Lunde et al. did not find an improvement in ejection fraction in patients with acute MI that were treated with stem cells. This might be explained by the fact that the method used to recover stem cells in this trial had a negative impact on their functional properties. Also the study by Jannsens and co-workers failed to show a beneficial effect of stem cell therapy on ejection fraction, most likely because the cells were administered to early after the index AMI. Because of the small size and the non-randomized nature of initial studies, a new trial, the Repair-AMI trial (Reinfusion of Enriched bone marrow Progenitor cells And Infarct Remodelling in Acute Myocardial Infarction) the largest, first double-blind, placebo-controlled, randomized multicenter study investigating the effects of reinfusion of enriched bone marrow progenitor cells on cardiac remodelling after acute myocardial infarction was initiated. This study clearly demonstrated that intracoronary infusion of bone marrow-derived progenitor cells partially prevents postinfarct heart failure due to a better preservation of left ventricular function and might be associated with a better long-term-prognosis. The exact mechanisms by which stem cells exert their effects in humans are not entirely clear however, the reconstitution of damaged endothelium might represent one of these mechanisms. Axel Linke noted that the positive effects of intracoronary stem cell therapy are not restricted to patients with acute myocardial infarction,, in patients with reperfused chronic ischemic heart disease, stem cell transplantation was also associated with an improvement in myocardial perfusion and metabolism, reduction in the amount of scar tissue, increase in left ventricular ejection fraction and exercise capacity. But what is the perspective for the future? Large, randomized multicenter trials are needed to show that stem cell therapy in patients with acute myocardial infarction and chronic myocardial ischemia beneficially influences morbidity and mortality at long-term follow-up.

Cardiac Stem Cell Therapy

Alexander Kaminski for Gustav Steinhoff (University of Rostock) presented his experience in the treatment of patients with chronic ischemic heart disease (IHD) with autologous human bone marrow progenitor cells. In a safety study involving patients with IHD, Gustav Steinhoff and co-workers were able to show that intramyocardial delivery of bone marrow-derived progenitor cells during coronary artery bypass surgery is associated with a significant improvement in left ventricular ejection fraction (LVEF) at 6 and 18 months of follow-up in the absence of harmful side effects. Based on these positive results, in a subsequent prospective

randomized controlled trial, 40 patients with IHD were treated by CABG alone or CABG and cell therapy. In the CABG + cell therapy group, LVEF increased by almost 10 % from 37.4±8.4 % at baseline to 47.1±8.3 % at 6 months, whereas patients treated by CABG were characterized by a gain in ejection fraction by less than 4 % from 37.9±10.3 % at baseline to 41.3±9.1 % at 6 months ($p<0.05$). The LVEF and myocardial perfusion was significantly better in the CABG + cell therapy group as compared to the CABG group at 6 months. In his summary, Alexander Kaminski pointed out that intramyocardial injection of bone marrow stem cells is safe and beneficial with regard to an improvement in myocardial perfusion and left ventricular performance. However, it remains to be established whether these effects are associated with a long-lasting clinical advantage. Additionally, further research is required to improve techniques of stem cell application, culture and modification in order to establish treatment conditions for congenital and adult cardiac diseases in the future, e.g. using tissue engineering.

Cardiovascular Tissue Engineering "Bench to Bedside"-Approaches

As the last speaker of the session, **Ulrich Martin for Axel Haverich** (Hannover Medical School) focused on "Bench to Bedside" approaches in cardiovascular tissue engineering. A major goal of tissue engineering is the reconstruction of inappropriately developed embryonic tissue or the complete or partial replacement of diseased organs in order to reestablish function. At present, researchers focus on the reconstruction of functional myocardium and valves. Despite recent progress, the replacement of myocardial scars by functional myocardium, which has been engineered in a bioreactor, is not clinical reality. This is largely due to the fact that mature, differentiated, adult cardiomyocytes do not grow in culture and, therefore, do no repopulate biological or synthetic scaffolds used as a matrix. However, this problem might be resolved by embryonic stem cells, but their widespread use is restricted due to ethical consideration and the problem of immune reaction with the host organism in the absence of immunosuppression. Additionally, an adequate blood supply to the engineered tissue is a prerequisite for long-term graft survival in vivo, but this has not been achieved in clinical settings. Nevertheless, the gain of knowledge allowed the development of matrices containing vascular structures supplying blood and nutrients to engineered tissue for replacement of right atrial and ventricular tissue in animals. In contrast, replacement of disease valves through engineered ones is already clinical reality.. These valves are produced by repopulating a biological matrix e.g. by endothelial progenitor cells from the recipient of the transplant. Pilot studies from Axel Haverich and co-workers suggest that these valves possess the ability to grow and adapt to the anatomical changes during childhood. Based on these findings, large clinical trials are designed or have already started to enroll patients in order to evaluate the long-term safety and efficacy of bioengineered heart valves in humans.