Universität Rostock Traditio et Innovatio

Universitätsmedizin Rostock

3rd EACTS/REMEDIC Meeting on Cardiac and Pulmonary Regeneration

Venue: **Berlin-Brandenburgische Akademie der Wissenschaften**
Jägerstraße 22/23, 10117 Berlin

Date: **December 13-15, 2012**

RTC Referenz- und Translationszentrum für kardiale Stammzelltherapie Universität Rostock

Index

1 Scientific report

1.1 Summary

The 3rd EACTS conference on cardiac and pulmonary regeneration was focused on presentations and discussions of latest developments in basic research and clinical translation in the field of cardiovascular and pulmonary regeneration. High-ranking scientists and renowned officials as well as young European researchers interactively discussed their results and new ideas.
A total of 37 abstracts were submitted and accepted. These were split into 12 oral presentations and 25 poster presentations. The selection committee consisted of G. Steinhoff, U. Martin, R. Schmid, H.J. Ankersmit and G. Karoubi. 35 abstracts are published in the issue of Interactive CardioVascular and Thoracic Surgery (ICVTS) in February 2013 (1). 16 key note speakers presented their latest results. The conference brought together international leading researchers as well as young European scientists. Of a total of 9 sessions, the first one, an international science talk about clinical prospect of cardiovascular regeneration, took place in the famous Rudolf Virchow lecture hall ruin of the Charité.

Talking about stem cell medicine: U. Martin, Hannover, Germany; J.P. Cooke, Stanford, USA; W. Sherman, New York, USA and G. Steinhoff, Rostock, Germany

1.2 Description of the scientific content of and discussion at the event

1.2.1 Science talk – clinical prospect of cardiovascular regeneration

A main focus of the scientific debate was the selection of optimal cells for cardiac cell transplantation and necessary controls for method evaluation. Whereas the impact of paracrine factors from transplanted cells or cell-derived conditioned media was widely recognized, researchers had controversial views on the impact of undifferentiated cell application and on the necessary depth of characterization for therapeutic use. Enhancement of therapeutic efficacy by cell pre-conditioning regimes was considered feasible but limited compared to the promise of genetic engineering; in any case: the need to clarify involved mechanisms was emphasized (1). Fruitful discussions developed on clinically applicable biopolymers and scaffolds for tissue engineering. The discussants emphasized improved test methods for tissue engineering constructs as well as promising data on large animal models and on the application of tissue engineered constructs generated from human cells; combination of this know-how may help to focus and speed up further studies in the field (1-2).

Discussions about evolving regulatory concerns revealed diverging practice in Europe and the US. The meeting provided excellent opportunities for basic and clinical researchers to gather information on clinical translation procedures and discuss their respective approaches together with regulatory affairs experts to make new therapies available to the patients.
Cell programming was generally considered to be a highly promising approach for the future. A model may be provided by dedifferentiation preceding of cardiac regeneration in zebrafish. Therefore, scientific exchange focused on the impact of specific pathways on dedifferentiation (Hedgehog, IGF) and cardiac differentiation (MESP-1, TGF-beta, YY-1) (3-6). First reports on selective generation of individual cardiac or pulmonary cell types (endothelial cells, pace maker cells, Clara cells) from pluripotent cells were given and discussed during the meeting (1). Genetic recombination techniques employed for fate-mapping, for cell-type specific cell destruction to generate optimal injury models, or for gene defect repair were considered by basic researchers as the most valuable methodological advancement (2-3). Data presented on reprogramming of cells from different sources led to fruitful discussions about non-viral transfection and cell selection approaches as well as labeling for non-invasive cell tracking (1, 4). Cell modification by small RNAs as well as cell-permeant peptides may allow for safer and gentler ways of reprogramming and were discovered to be connected to particular cellular pathways. New findings on the involvement of cellular innate immunity may be exploited for highly efficient reprogramming while eliminating the need of viral vectors (7).

1.2.2 Basic science

Basic science aims to investigate cardiac regeneration mechanisms of the injured heart. One widely used model is the lower vertebrate zebrafish. This is special, as its heart muscle regeneration is achieved without stem cells, instead, mature heart muscle cells regress to a stem cell-like state and redifferentiate (8). Therefore it is important to evaluate the principles of underlying regenerative capacity.
Choi and coworkers employed fluorescent ubiquitylation-based cell cycle indicator (FUCCI) technology to identify several small molecules that increase or reduce cardiomyocyte proliferation during heart development (3). Here signaling pathways via hedgehog, insulin-like growth factor or transforming growth β are involved (3) and can be pharmacologically modulated to manipulate cardiomyocyte proliferation during adult heart regeneration (3).
Another important finding was presented by R. David, demonstrating that the earliest events initiating cardiogenesis are conserved between higher and lower vertebrates with MespA being the functional amphibian homolog to mammalian Mesp1 *in vivo* (9).

1.2.3 Stem cell science and technology

Stem cells are the basis for regeneration in medicine, differentiating into the required cell types. Therefore it is necessary to investigate differentiation potential of pluripotent and induced pluripotent stem (iPS) cells.
The group of R. Zweigerdt developed a forward programming protocol to obtain human pluripotent stem cells by conventional plasmid transfection without viral vectors. Here a combination of *BAF60C*, *GATA4*, and *MESP1* or even of *GATA4*, and *MESP1* transcription factors is sufficient to generate cardiomyocytes (4). Therapeutic application of stem cell technology requires large cell quantities generated under defined conditions. Thus upscaling procedures need to be established. Zweigerdt and coworkers developed a mini stirred bioreactor of 100 ml cell culture volume and could demonstrate the ability of cells to differentiate into derivates of all three germ layers and maintained expression of pluripotency markers *in vitro* (10).

Also, iPS cell derived cardiovascular progenitor cells have the capability to form myocardial cells and are therefore suitable for myocardial regenerative therapy. To prove their capacity to ameliorate cardiac function Rojas investigated murine iPSC-derived cardiovascular progenitor population expressing the surface marker foetal liver kinase-1 (Flk-1) after acute myocardial infarction in mice (11). Indeed iPS cell-derived Flk-1(pos) progenitor cells differentiate into cardiovascular lineages *in vitro* and *in vivo* and improve cardiac function (11).

1.2.4 Tissue engineering technology

A Tissue engineered product contains or consists of engineered cells or tissues and is used in human beings to regenerate, repair or replace a human tissue. Thereby the purpose is to understand the principles of tissue growth and to implement this into humans to yield functional benefit (12-13).
Qian and coworkers could show *in vivo* that murine cardiac fibroblasts are directly reprogrammed in their native environment into cardiomyocyte-like cells via the addition of Gata4, Mef2c and Tbx5. This demonstrated successful *in vivo* reprogramming for potential regenerative purposes in injured mouse hearts, resulting in reduced scar formation and improved cardiac function (13).
The group of Zimmermann demonstrated a protocol for cardiac differentiation of human embryonic stem cells and the assembly of these cardiomyocytes into engineered heart muscle (14). This protocol may easily be adapted to other stem cell-derived cardiomyocytes, like iPSC (14).
Another approach to regenerate ischemic damaged hearts was investigated by the group of G. Steinhoff, who used systemic delivery of adenoviral vectors encoding human VEGF combined with magnetic nanobeads in a rat myocardial infarction model under the control of an external magnetic field (15). This increased VEGF expression in the infracted heart and lead to neovascularization and improved post-infarction recovery of LV function (15). Thus, an improved gene therapy with the potential into clinical applications was revealed.

1.2.5 Lung regeneration

Lung regeneration due to disorders of the respiratory system is usually quite minimal. Therefore adequate therapies need to be established and latest research findings seem to be promising.
A. Perl *et al*. found out that crosstalk between epithelial and mesenchymal cells regulates the fibroblast phenotypes during alveolar septation. Further results indicate that induction of Peroxisome proliferator-activated receptor-χ signaling and inhibition of Fibroplast Growth factor receptor 2 signaling changes the expression of genes being important for epithelial-mesenchymal crosstalk during early development of the lung (16).
Cortes-Diercks and colleagues stated a paracrine-based anti-tumor effect of human lung MSC culture media in malignant pleural mesothelioma cell lines (MPM) based on the fact that cell proliferation and cell viability were significantly reduced in MPM. These findings may also indicate a potential therapeutic role in those tested cell lines (1).
C. Mauritz *et al*. investigated the generation and differentiation process of human and murine pluripotent stem cells into airway epithelial cells. Among other findings it was shown that the application of key differentiation factors induced the appearance of airway epithelia cells in those cultures. Also these results might represent a further step towards the development of therapies for pulmonary diseases (1).

1.2.6 Cardiovascular regeneration

Shortly after birth cardiac muscle cells almost exit the cell-division cycle and divide only rarely (17). Heart attack leads to dying of a billion cardiomyocytes, with little capacity to regenerate these cells. Thus, heart function is compromised and may induce heart failure or even sudden death (17). Therefore basic researchers and clinicians investigate the possibilities to induce cardiomyocyte regeneration.
The group of T. Braun investigates the phenomenon of dedifferentiation as a potential tool in

cardiac regenerative processes, which is mostly known in plants and amphibians (e.g. initiated replacement of lost body parts). Activation of the cytokine oncostatin M signaling pathway initiates dedifferentiation of cardiomyocytes both *in vitro* and *in vivo* and thereby protects the heart from acute myocardial ischemia (18). However, continuous oncostatin M activation promotes dilative cardiomyopathy (18). Thus, continuous activation or malfunctions of the cellular dedifferentiation machinery might contribute to different disease conditions.
Kensah and coworkers revealed in a proof-of-concept study the use of iPS- and ES-cell-derived cardiomyocytes to generate three-dimensional aggregates, which act as functional bioartificial tissue, so called cardiac bodies (19). Direct fusion of these cardiac bodies resulted in structurally and functionally homogenous syncytium, which requires the following factors: addition of fibroblasts, ascorbic acid supplementation and increased static stretch (19). This system allows novel insight into cardiac tissue formation and maturation, with potential impact on new concepts for myocardial repair.
Cardiac regeneration is also enhanced by laser-based cell printing of human umbilical vein endothelial cells (HUVEC) and human MSC in a defined pattern on a Polyester urethane urea cardiac patch (2). The group of Steinhoff demonstrated *in vivo* enhanced angiogenesis in the border zone of infarction and preserved cardiac functions after acute myocardial infarction (2). This technology might improve wound healing und functional preservation.

1.2.7 Clinical translation-regulatory framework and GxP

Clinical translation is an essential tool to transfer latest research findings into humans whereas again specific questions may arise that need to be considered in laboratory experiments. Safety and efficacy of new therapeutic approaches need to be evaluated and strictly documented in clinical studies according to regulatory guidelines. Therefore Good Clinical Praxis (GCP) is a legal standard to perform these trials. S. Sethe, an expert in regulatory affairs for cell and tissue based therapies in Europe and the USA, gave a very clear and graspable introduction into the topic and among others he also pointed out non clinical research including animal experiments to be mandatory before starting clinical studies (20). Furthermore A. Kaminski, surgeon and one of the investigators of the phase III trial PERFECT, stated his view of clinical aspects in the context of this crucial translation process from bench to bedside. Besides general remarks to recent studies investigating safety and efficacy of stem cell therapy after myocardial infarction he also explained molecular cell mechanisms that occur while these events happen (e.g. fragmentation of gab junctions between neighboring cells). Additionally U. Ruch, a translation manager, introduced a Cardiac Stem Cell Registry that is currently being tested and supposed to become an essential tool to establish high quality standards regarding all future heart stem cell applications in Germany/Europe (21).

1.2.8 Paracrine factors

J.H. Ankersmit presented data on peripheral blood mononuclear cells as easily accessible autologous source of regenerative factors. Cell-free supernatants generated *in vitro* from short-term cultivated monocytes promoted healing of cutaneous wounds in pigs. The freeze-dried secretome of apoptotic leukocytes, applied intramyocardially via a balloon catheter technique (NOGA), improved cardiac function in a porcine model of reperfused myocardial infarction (22). Cell-free regenerative concentrates such as employed by Ankersmit and by Di Santo, who focus on factors secreted by endothelial progenitor cells for treatment of ischaemia, contain a multitude of proteins, peptides and possibly nucleic acids. Despite the fact that their composition has not yet been characterized in detail and factors responsible for the regenerative activity, first application in patients was performed and reported to be successful. Immunosuppression of apoptotic cell paracrine factors could be important for the effect; Lichtenauer *et al*. showed an increase in perfusion as well as reduced necrosis in infracted rat hearts after injection of anti-thymocyte-globulin as representative immunosuppressive agent (23).

1.2.9 Regenerative cardiovascular medicine update and future development

The group around E. Delyagina is using the polymer polyethylenimine (PEI) coated magnetic nanoparticle for plasmid DNA (pDNA) transfection *in vitro* and *in vivo* since 2008 (1). With this technique a significantly higher transfection than with commercially available polyplexes could be shown in human mesenchymal stem cells. The results demonstrated a more rapid and efficient release of pDNA in the perinuclear region (1).

Merkert and his team had succeeded the generation of patient specific iPS cells from endothelial cells of peripheral blood (1). For the introduction of target genes in the iPS cells, they established a zinc finger nucleases (ZFN) based gene targeting protocol with transfection efficiency of up to 1%. With this approach, the aim of a functional correction be pursued in the CF disease (1).

Research approaches of Cooke *et al.* demonstrate efficient induction of pluripotency by viral or mRNA due to the toll-like receptor 3 (TLR3). TLR3 part of the innate immunity that's activation is of importance to successful nuclear reprogramming (7).

1.3 Assessment of the results and impact of the event on the future directions of the field

On the 3rd EACTS conference cardiac and thoracic surgeons, basic, clinical and industrial scientists, as well as young European researches presented and interactively discussed their latest developments in the field of cardiovascular and pulmonary regeneration, supported by experts in regulatory affairs. This resulted in expanded knowledge in basic and applied science and translational medicine (GMP, GLP, GCP) for the development of new concepts in stem cell therapy for every participant. Moreover during the poster session and within the breaks there were lively and fruitful discussions about the presented topics regarding pharmacological, tissue engineering and stem cell therapy concepts in cardiac and pulmonary regeneration. These discussions lead to further cooperation and scientific exchange between the participants.

In cardiovascular and pulmonary medicine autologous stem cell therapy is already performed since more than 10 years. The field recently expanded on new research progress with ES and iPS cells. This became also apparent at the conference, where several talks and poster presentations underlined the relevance of these cells in cardiac and pulmonary regeneration. The innovative potential of this new approach (turning mature cells into stem cells) is also emphasized by the Nobel Prize in physiology or medicine in 2012.

Bringing innovative approaches into new therapies is subject to diverse regulatory requirements. Therefore the conference revealed the importance to consider clinical implementation and regulatory pathways already at the very beginning in basic science. Therefore, translational aspects are very important for the fast development and a crucial factor for clinical success

1.4 Annexes: programme of the meeting and full list of speakers and participants

1.5 References

1. Bader A, Brodarac A, Hetzer R, Kurtz A, Stamm C, Baraki H, Kensah G, Asch S, Rojas S, Martens A, Gruh I, Haverich A, Kutschka I, Cortes-Dericks L, Froment L, Kocher G, Schmid RA, Delyagina E, Schade A, Scharfenberg D, Skorska A, Lux C, Li W, Steinhoff G, Drey F, Lepperhof V, Neef K, Fatima A, Wittwer T, Wahlers T, Saric T, Choi YH, Fehrenbach D, Lehner A, Herrmann F, Hollweck T, Pfeifer S, Wintermantel E, Kozlik-Feldmann R, Hagl C, Akra B, Gyöngyösi M, Zimmermann M, Pavo N, Mildner M, Lichtenauer M, Maurer G,

Ankersmit J, Hacker S, Mittermayr R, Mildner M, Haider T, Nickl S, Zimmermann M, Beer L, Lebherz-Eichinger D, Schweiger T, Mitterbauer A, Keibl C, Werba G, Frey M, Ankersmit HJ, Herrmann S, Lux CA, Steinhoff G, Holfeld J, Tepeköylü C, Wang FS, Kozaryn R, Schaden W, Grimm M, Wang CJ, Holfeld J, Tepeköylü C, Kozaryn R, Urbschat A, Zacharowski K, Grimm M, Paulus P, Avaca MJ, Kempf H, Malan D, Sasse P, Fleischmann B, Palecek J, Dräger G, Kirschning A, Zweigerdt R, Martin U, Katsirntaki K, Haller R, Ulrich S, Sgodda M, Puppe V, Duerr J, Schmiedl A, Ochs M, Cantz T, Mall M, Martin U, Mauritz C, Kensah G, Lara AR, Dahlmann J, Zweigerdt R, Schwanke K, Hegermann J, Skvorc D, Gawol A, Azizian A, Wagner S, Krause A, Dräger G, Ochs M, Haverich A, Gruh I, Martin U, Klopsch C, Gaebel R, Kaminski A, Chichkov B, Jockenhoevel S, Steinhoff G, Klose K, Roy R, Brodarac A, Kang KS, Bieback K, Nasseri B, Choi YH, Kurtz A, Stamm C, Lepperhof V, Polchynska O, Kruttwig K, Brüggemann C, Xu G, Drey F, Neef K, Saric T, Lichtenauer M, Werba G, Mildner M, Baumgartner A, Hasun M, Nickl S, Beer L, Mitterbauer A, Zimmermann M, Gyöngyösi M, Podesser BK, Ankersmit HJ, Ludwig M, Tölk A, Skorska A, Noack T, Steinhoff G, Margaryan R, Assanta N, Menciassi A, Burchielli S, Matteucci M, Lionetti V, Luchi C, Cariati E, Coceani F, Murzi B, Martens A, Rojas SV, Kensah G, Rotärmel A, Baraki H, Haverich A, Martin U, Gruh I, Kutschka I, Nasseri BA, Klose K, Ebell W, Dandel M, Kukucka M, Gebker R, Choi YH, Hetzer R, Stamm C, Paulus P, Holfeld J, Urbschat A, Mutlak H, Ockelmann P, Tacke S, Zacharowski K, Scheller B, Pereszlenyi A, Rojas SV, Martens A, Baraki H, Schwanke K, Zweigerdt R, Martin U, Haverich A, Kutschka I, Rojas SV, Martens A, Meier M, Baraki H, Schecker N, Rathert C, Zweigerdt R, Martin U, Haverich A, Kutschka I, Roy R, Brodarac A, Kukucka M, Kurtz A, Becher PM, Choi YH, Drori-Carmi N, Bercovich N, Zahavi-Goldstein E, Jack M, Netzer N, Pinzur L, Chajut A, Tschöpe C, Stamm C, Ruch U, Kaminski A, Strauer BE, Tiedemann G, Steinhoff G, Schade A, Delyagina E, Scharfenberg D, Lux C, Steinhoff G, Schlegel F, Dhein S, Akhavuz O, Mohr FW, Dohmen PM, Schlegel F, Salameh A, Oelmann K, Kiefer P, Dhein S, Mohr FW, Dohmen PM, Schwanke K, Merkert S, Templin C, Jara-Avaca M, Müller S, Haverich A, Martin U, Zweigerdt R, Skorska A, von Haehling S, Ludwig M, Slavic S, Curato C, Altarche-Xifro W, Unger T, Steinhoff G, Li J, Zhang Y, Li WZ, Ou L, Lux CA, Ma N, Steinhoff G, Haase A, Alt R, Schwanke K, Martin U. 2012. *3rd EACTS Meeting on Cardiac and Pulmonary Regeneration Berlin-Brandenburgische Akademie, Berlin, Germany, 14-15 December 2012.* Interact Cardiovasc Thorac Surg.16(2):S227-36.

2. Gaebel R, Ma N, Liu J, Guan J, Koch L, Klopsch C, Gruene M, Toelk A, Wang W, Mark P, Wang F, Chichkov B, Li W, Steinhoff G. 2011. *Patterning human stem cells and endothelial cells with laser printing for cardiac regeneration.* Biomaterials. 32(35):9218-30.
3. Choi WY, Gemberling M, Wang J, Holdway JE, Shen MC, Karlstrom RO, Poss KD. 2013. *In vivo monitoring of cardiomyocyte proliferation to identify chemical modifiers of heart regeneration.* Development. 140(3):660-6.
4. Hartung S, Schwanke K, Haase A, David R, Franz WM, Martin U, Zweigerdt R. 2013. *Directing Cardiomyogenic Differentiation of Human Pluripotent Stem Cells by Plasmid-Based Transient Overexpression of Cardiac Transcription Factors.* Stem Cells Dev.
5. Chen WP, Wu SM. 2012. *Small molecule regulators of postnatal Nkx2.5 cardiomyoblast proliferation and differentiation*. J Cell Mol Med. 16(5):961-5
6. Gregoire S, Karra R, Passer D, Deutsch MA, Krane M, Feistritzer R, Sturzu A, Domian I, Saga Y, Wu SM. 2013. *Essential and Unexpected Role of YY1 to Promote Mesodermal Cardiac Differentiation.* Circ Res.
7. Lee J, Sayed N, Hunter A, Au KF, Wong WH, Mocarski ES, Pera RR, Yakubov E, Cooke JP. 2012. *Activation of Innate Immunity Is Required for Efficient Nuclear Reprogramming.* Cell 152(3):547-558.
8. Choi WY, Poss KD. 2012. *Cardiac regeneration*. Curr Top Dev Biol. 100:319-44.
9. Kriegmair MC, Frenz S, Dusl M, Franz WM, David R, Rupp RA. 2012. *Cardiac differentiation in Xenopus is initiated by mespa.* Cardiovasc Res.
10. Olmer R, Lange A, Selzer S, Kasper C, Haverich A, Martin U, Zweigerdt R. 2012. *Suspension*

culture of human pluripotent stem cells in controlled, stirred bioreactors. Tissue Eng Part C Methods. 18(10):772-84.
11. Mauritz C, Martens A, Rojas SV, Schnick T, Rathert C, Schecker N, Menke S, Glage S, Zweigerdt R, Haverich A, Martin U, Kutschka I. 2011. *Induced pluripotent stem cell (iPSC)-derived Flk-1 progenitor cells engraft, differentiate, and improve heart function in a mouse model of acute myocardial infarction*. Eur Heart J.; 32(21):2634-41.
12. Langer R, Vacanti JP. 1993. *Tissue engineering*. Science. 260(5110):920-6.
13. Qian L, Huang Y, Spencer CI, Foley A, Vedantham V, Liu L, Conway SJ, Fu JD, Srivastava D. 2012. *In vivo reprogramming of murine cardiac fibroblasts into induced cardiomyocytes.* Nature. 485(7400):593-8.
14. Soong PL, Tiburcy M, Zimmermann WH. 2012. *Cardiac differentiation of human embryonic stem cells and their assembly into engineered heart muscle*. Curr Protoc Cell Biol.
15. Zhang Y, Li W, Ou L, Wang W, Delyagina E, Lux C, Sorg H, Riehemann K, Steinhoff G, Ma N. 2012. *Targeted delivery of human VEGF gene via complexes of magnetic nanoparticle-adenoviral vectors enhanced cardiac regeneration*. PLoS One. 7(7):e39490.
16. Chen L, Acciani T, Le Cras T, Lutzko C, Perl AK. 2012. *Dynamic regulation of platelet-derived growth factor receptor α expression in alveolar fibroblasts during realveolarization.* Am J Respir Cell Mol Biol. 47(4):517-27
17. Mercola M. 2012 *Cardiovascular biology: A boost for heart regeneration*. Nature. 492(7429):360-2.
18. Pöling J, Gajawada P, Lörchner H, Polyakova V, Szibor M, Böttger T, Warnecke H, Kubin T, Braun T. 2012. *The Janus face of OSM-mediated cardiomyocyte dedifferentiation during cardiac repair and disease.* Cell Cycle. 11(3):439-45.
19. Kensah G, Roa Lara A, Dahlmann J, Zweigerdt R, Schwanke K, Hegermann J, Skvorc D, Gawol A, Azizian A, Wagner S, Maier LS, Krause A, Dräger G, Ochs M, Haverich A, Gruh I, Martin U. 2012. *Murine and human pluripotent stem cell-derived cardiac bodies form contractile myocardial tissue in vitro*. Eur Heart J.
20. Tiedemann G, Sethe S. 2011. *Regulatory Frameworks for Cell and Tissue Based Therapies in Europe and the USA.* Regenerative Medicine – from protocol to patient, Ed: Gustav Steinhoff, Springer Netherlands.
21. Ruch U, Kaminski A, Strauer BE, Tiedemann G, Steinhoff G. 2013. *Cardiac Stem Cell Registry: A Tool to establish standardization and quality assurance in Germany and even in Europe?* ICVTS 16(2):227-236.
22. Lichtenauer M, Mildner M, Hoetzenecker K, Zimmermann M, Podesser BK, Sipos W, Berényi E, Dworschak M, Tschachler E, Gyöngyösi M, Ankersmit HJ. 2011. *Secretome of apoptotic peripheral blood cells (APOSEC) confers cytoprotection to cardiomyocytes and inhibits tissue remodelling after acute myocardial infarction: a preclinical study*. Basic Res Cardiol. 106(6):1283-97.
23. Lichtenauer M, Mildner M, Werba G, Beer L, Hoetzenecker K, Baumgartner A, Hasun M, Nickl S, Mitterbauer A, Zimmermann M, Gyöngyösi M, Podesser BK, Klepetko W, Ankersmit HJ. 2012. *Anti-thymocyte globulin induces neoangiogenesis and preserves cardiac function after experimental myocardial infarction.* PLoS One.7(12):e52101.

2 Financial report

See attached

3 List of participants

See attached

3rd EACTS meeting on Cardiac and Pulmonary Regeneration

Berlin, Dec. 13-15, 2012

Organizer: G. Steinhoff
CoOrganizer: U. Martin

December 13, 2012		
Till 7 p.m.	Arrival, registration Get together	
Time 7:30 p.m.	Session: Science talk – Clinical Prospect of Cardiovascular Regeneration	**Gustav Steinhoff,** Rostock, Germany **John P. Cooke**, Stanford, USA **Warren Sherman**, New York, USA **Ulrich Martin**, Hannover, Germany
December 14, 2012		
08:00-09:00	Arrival, registration	
09:00-10:30 a.m.	Basic Science	Chair: John P. Cooke and Joseph Gold, Stanford 09:00 – 9:30 a.m. **Wen-Yee Choi**, Durham, USA Mechanisms of cardiac regeneration – learning from zebrafish 09:30 – 10:00 a.m. **Chi-Chung Wu** , Ulm, Germany Heart regeneration in zebrafish 10:00 – 10:30 a.m. **Robert David**, Rostock/Munich, Germany Cardiac differentiation in Xenopus is initiated by xMespA
10:30 – 10:45 a.m.	Coffee break	
10:45-12:00 a.m.	Stem cell science and technology	Robert David, Rostock 10:45 – 11:15 a.m. **Sean M. Wu,** Stanford, USA Cardiovascular cell differentiation 11:15 – 11:45 a.m. **Robert Zweigerdt**, Hannover, GER Cardiac differentiation of pluripotent stem cells and upscaling technologies 11:45 – 12:00 a.m. **S.V. Rojas**, Hannover, GER Magnetic resonance imaging and bioluminescence signal assessment for evaluation of biodistribution, vitality and proliferation of induced pluripotent stem cells (iPs) following transplantation in heart failure
12:00 a.m. – 1 p.m.	Lunch break – Poster session 1	
1:00-2:30 p.m.	Tissue engineering Technology	Chair: Robert Zweigerdt, Hannover

		1:00 – 1:30 p.m. **Li Qian,** UCSF, USA Directed programming technology 1:30 – 2:00 p.m. **W Zimmermann,** Goettingen, GER Applications of engineered heart tissue 2:00 – 2:15 p.m. **Y Zhang**, Rostock, GER Targeted delivery of human VEGF gene via complexes of magnetic nanoparticle-adenoviral vectors enhanced cardiac regeneration 2:15 – 2:30 p.m. **F Schlegel**, Leipzig, GER An injectable tissue engineered heart valve for right ventricular outflow tract recnostruction in a mini-pig model
2:30-3:30 p.m.	Lung regeneration	Chair: Ralph Schmid, Berne and Ulrich Martin, Hannover 2:30 – 3:00 p.m. **Anna Karina Perl,** Cincinnati Lung fibroblasts and regeneration 3:00 – 3:15 p.m. **L Cortes-Dericks**, Bern, SWISS Lung Mesenchymal Stem Cell-Conditioned Medium Shows Anti-Tumour Effect in a Malignant Pleural Mesothelioma Cell Line, H28 3:15 – 3:30 p.m. **C Mauritz/ KK Katsirnthaki**, Hannover, GER Optimized differentiation protocols for the generation of murine and human pluripotent stem cells into respiratory epithelial cells
3:30-4:30 p.m.	Coffee Break – Poster session 2	
4:30-6:00 p.m.	Cardiovasular regeneration	Chair: Sean Wu, Stanford 4:30 – 5.00 p.m. **Thomas Braun**, Bad Nauheim, GER Cardiomyocyte de-differentiation and growth factor signaling during cardiac repair and disease 5:00 – 5:15 p.m. **G Kensah**, Hannover, GER Murine and human pluripotent stem cell-derived cardiac bodies form contractile myocardial tissue in vitro 5:15 – 5:30 p.m. **F Drey**, Cologne, GER Improved recovery of heart function by co-

		transplantation of iPS cell-derived cardiomyocytes with mesenchymal stem cells. 5:30 – 5:45 p.m. **R Gaebel**, Rostock, GER Laser-based cell printing of HUVEC and HMSC on a cardiac patch and implantation after myocardial infarction in rats. 5:45 – 6:00 p.m. **K Klose**, Berlin, GER Heart failure serum cytokines impair activity and proliferation of neonatal stem cells.
7:00-9:00	Social Event	

December 15, 2012		
09:00-10:30 a.m.	Clinical translation-regulatory framework and GxP	Chair: Warren Sherman, New York 09:00 – 09:30 a.m. **Joseph Gold,** Stanford, USA ES-cells: Cardiac cell therapy 09:30 – 10:00 a.m. **Alexander Kaminski,** Rostock, GER Application of adult stem cells in cardiac surgery 10:00 – 10:30 a.m. **Sebastian Sethe,** Durham, UK Regulatory frameworks in Europe and USA
10:30 – 10:45	Coffee break	
10:45-12:00	Paracrine factors	Chair: Jan Henrik Ankersmit, Vienna 10:45 – 11:15 a.m. **Jan Henrik Ankersmit**, Vienna, AUSTRIA APOSEC - PBMC and Cell Regeneration 11:15 – 11:45 a.m. **S Di Santo**, Bern, SWISS EPC Secretomes and ischaemia 11:45 – 12:00 a.m. **M Lichtenauer**, Jena, GER Anti-thymocyte globulin induces neoangiogenesis and preserves cardiac function after expertimental myocardial infarction
12:00-12:30 p.m.	Lunch break – Poster session 3	
12:30-2:00 p.m.	Regenerative Cardiovascular Medicine update and future development	Chair: Gustav Steinhoff, Rostock and Ulrich Martin, Hannover 12:30 – 1:00 p.m. **John P. Cooke**, Stanford, USA A closer view on angiogenesis in peripheral artery

		disease 1:00 – 1:30 p.m. **Warren Sherman**, USA What standards are required for clinical translation? 1:30 – 1:45 p.m. **E Delyagina**, Rostock, GER Non-viral transfection in human mesenchymal stem cells via magnetic nanoparticles: efficient DNA release in the perinuclear region 1:45 – 2:00 p.m. **S Merkert,** Hannover, GER Generation of CF-Patient derived IPS cells and efficient ZFN-based gene targeting in transgenic human IPS cells

Poster Sessions

December 14, 2012	
12:00 a.m. – 1 p.m.	Lunch break – Poster session 1

Chair: Alexander Kaminski, Rostock

Basic Science / Stem cell science and technology / Tissue engineering Technology

H Baraki, Hannover , Germany
Intramyocardial transplantation of bioartificial cardiac tissue for restauration of infarcted myocardium in rats

D Fehrenbach, Munich, Germany
The effect of colonized cells on the mechanical properties of synthetic scaffolds.

S Herrmann, Rostock, Germany
CD271 upregulation by hypoosmolar preconditioning of human bone marrow-derived cells

M Jara- Avaca, Hannover,Germany
Small molecule-based selective enrichment of cardiomyocytes

V Lepperhof, Cologne, Germany
Generation of luminescent iPS cell-derived cardiomyocytes for *in vivo* monitoring of survival efficiency after cardiac transplantation

C Klopsch, Rostock, Germany
Spray- and laser-assisted biomaterial processing for intraoperative table-side autologous heart valve tissue engineering

A Martens, **S.V. Rojas,** Hannover, Germany
Purified induced pluripotent stem cell (iPSC)-derived cardiomyocytes engraft and improve remodeling and ventricular function after myocardial infarction in mice.

R Roy, Berlin, Germany
Placenta-derived mesenchymal stromal cells for cardiac cell therapy post myocardial infarction

F Schlegel, Leipzig, Germany
Can bone marrow stem-cells be transformed into venous endothelial cells for cardiovascular tissue engineering?

K Schwanke, Hannover, Germany
Fast and Efficient multi-transgenic modification of human pluripotent stem cells

3:30-4:30 p.m.	Coffee Break – Poster session 2

Chair: Christof Stamm, Berlin

Tissue engineering Technology / Lung regeneration / Cardiovascular regeneration

A Bader, Berlin, Germany
Factors released by CD133pos cells from human bone marrow enhance survival of HL-1 cardiomyocytes under simulated ischemia

J Holfeld, Innsbruck, Austria
Shock wave treatment for recruitment of circulating CD31/ CD34 positive endothelial cells to ischemic muscle in rats: implications on vasculogenesis

J Holfeld, Innsbruck, Austria
Shock wave therapy differentially activates endothelial cells – Implications on the control of inflammation

M Ludwig, Rostock, Germany
Identification of Whole-Cell Currents of Murine $CD117^{+}$ Bone Marrow Stem Cells and Action of AT2R Stimulation

R Margaryan, Massa, Italy
Aortic stop-flow: A novel approach for selective perfusion of the coronary vascular bed in preterm fetus

P Paulus, Frankfurt am Main, Germany
Prednisolone enhances anti-inflammatory properties of graft macrophages in an orthotopic rat lung transplantation model

A Pereszlenyi
Reconstruction of the deep posttraumatic tracheal stenosis with the new lung-assist-system´s support

A Skorska, Rostock, Germany
The CD4+AT2R+ T cell subpopulation in response to ischemic heart injury

Alexandra Haase, Hannover, Germanmy
Highly efficient reprogramming of $CD34^+$ hematopoietic stem cells isolated from long term cryopreserved cord blood and differentiation into cardiomyocytes

December 15, 2012

12:00-12:30 p.m.	Lunch break – Poster session 3

Chair: Robert Zweigerdt, Hannover

Clinical translation-regulatory framework and GxP / Paracrine factors / Regenerative Cardiovascular Medicine update and future development

M Gyöngyösi, Vienna, Austria
Effect of percutaneous intramyocardial delivery of secretome of apoptotic white blood cells (APOSEC) on myocardial viability and function in experimental ischemic cardiomyopathy.

S Hacker, Vienna, Austria
Regenerative effects of secreted factors derived from peripheral blood mononuclear cells in cutaneous wound healing after full-thickness skin defects, burn and skin grafting: results of animal studies.

B A Nasseri, Berlin, Germany
Improved regional contractile function and reduced scar size after clinical cell therapy with CD133-positive cells

S.V. Rojas, Hannover, Germany
Cardiac transplantation efficiency of induced pluripotent stem cells (iPs) is improved by a fibrinogen matrix in an experimental model of ischemic heart failure

U Ruch, Rostock, Germany
Cardiac stem cell registry – a tool to establish standardization and quality assurance in Germany and even in Europe?

A Schade, Rostock, Germany
An innovative non-viral strategy for efficient microRNA delivery in human mesenchymal stem cells for regenerative medicine

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1 panel discussion
16 keynote lectures
12 selected oral presentations
25 Poster presentations