The Regrowing Heart
RTC-Report 2008-2014
Reference- and Translation Center for Cardiac Stem Cell Therapy (RTC)
University Rostock Medical Center
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In this report the Reference and Translation Center for Cardiac Stem Cell Therapy (RTC) at Rostock University introduces itself: for seven years the RTC has been home to an international team of scientists and clinicians who are committed to conducting high-performance medicine on cardiovascular diseases striving the therapeutic approach “Healing by Regeneration”. Until recently, the human heart has been regarded as not capable of regeneration in particular after myocardial infarction. Our work and other publications have been able to disprove this position. Even if novel therapies for heart regeneration after diseases are at an early stage of development, recently acquired advanced understanding from basic research on stem cells and cell programming makes the vision of the renewable heart real in the foreseeable future. The RTC has been established as a translation center for this pathway.

Foundation, goals and strategy of the RTC
The RTC was founded in 2008 on the initiative of Prof. Dr. Gustav Steinhoff, heart surgeon and scientist at the University Medical Center Rostock. We successfully convinced both the federal (BMBF) and the state government (M-V) as well as our industry partners of the general idea, goals and strategy of the RTC enabling the foundation of the RTC based on various sources of funding.

Preface

The RTC
- has the vision of the “Regrowing heart” – That’s what our research is aiming for
- pursues a strategy of translation improvement - we want to provide patients with novel and improved quality assured standardized healing options with regenerative properties
- aims for positioning itself as a Reference Center for cardiovascular stem cell therapy. Based on our quality standards we intend to be active in the formulation of general guidelines and the RTC plans to offer services for corresponding compliance.

Seven years RTC – a success story

„The generation of specific cardiomyocytes by means of the so-called cell programming is an important field of research. With this, our team has recently succeeded to generate high-purity mouse pacemaker cells. We will adapt this methodology to human cells. At the same time, the principle of this method will also be applied to obtain ventricular cardiac muscle cells. “

Prof. Dr. rer. nat. Robert David
Reference and Translation Center for Cardiac Stem Cell Therapy (RTC) at Rostock University
Clinic and Polyclinic for Heart Surgery at Rostock University Medical Center
Core elements of the RTC
The RTC resides in the rooms of the Biomedical Research Center (BMFZ) Rostock, a location where research and development groups of the University work side by side with companies.

The RTC is one of the five Translation Centers for Regenerative Medicine in Germany funded by the Federal and State Governments. The RTC distinguishes itself from the other centers by

- exclusively focusing on the cardiovascular field
- benefiting from relevant previous results and important contacts to industry
- the fact that a therapeutic “vision” did already exist at the time of foundation
- working together goal oriented since the group is relatively small and both the laboratory and clinic are under one leader
- implementing our research in clinical practice by means of a professional translation management

Seven years of successful research and development activities
The RTC can now refer to seven years of successful research and development activities on stem cells and cardiac regeneration.

The following Report introduces the RTC, gives a detailed impression of the research and development activities on stem cells and cardiac regeneration of the RTC, explains approaches for translation to the clinic, describes the development of the latest stem cell modification technologies to improve the efficacy of therapies and to subsequently increase the benefit for patients. Finally, the report summarizes the most important facts and figures.

Activities of the RTC
In the laboratories of the RTC innovative regenerative therapies have been investigated and developed by applying the latest molecular and cell-biological methods. Subject to highest safety standards promising therapeutic approaches are being tested for safety and efficacy in human beings by authorized clinical trial investigators in the heart surgical clinic. After translation to the clinic and subsequent evaluation of all data and results by the competent authorities and subsequent positive decision (authorization) the therapies will be applied to the patient care. The health status of all patients treated with our advanced therapies is followed up for the rest of their lifetimes. Relevant data are documented in a register to gain insight into long-term effects and are subsequently used for the optimization of novel therapeutic approaches.

“The RTC provides a gold standard to aspire for researchers from Brazil and abroad, and in the year of the 2014 FIFA World Cup we should not forget the name of the head (and captain) of the RTC, Doctor Steinhoff.”

Katherine de Carvalho, MD, PhD
Cell Therapy and Biotechnology in Regenerative Medicine Research
The Pelé Pequeno Príncipe Institute - Child and Adolescent Health Research - Associated Professor of Bioprocess Engineering and Biotechnology - Parana Federal University-Brazil
They gave me the hope to continue fighting and looking for new possibilities in order to achieve an improvement.

Dieter Magermann, Guatemala
Stem cell patient

Interview with Professor Dr. Gustav Steinhoff

„The regrowing heart is my vision“

What do Ivenacker oak trees and zebrafish have to do with your research?
Prof. Dr. Gustav Steinhoff: The Ivenacker oak trees are an impressive cultural- and natural-historical peculiarity in Germany. We assume that the oak trees are about 800 to 1200 years old. They have only been able to survive because they have adapted to their environment by regenerative mechanisms. The zebrafish is able to renew relevant organs. The heart of the zebrafish can reproduce tissue within a very short time. We learn from these natural phenomena and try to transfer corresponding insights to medical research.

The heart is your area of expertise. Once Udo Lindenberg sang about ...
Prof. Dr. Gustav Steinhoff: “You cannot repair a heart”. Udo Lindenberg was right. But, the regrowing heart is my vision. I work on it with all my heart.

You have once described Regenerative Medicine as the research field of the 21st century. Why?
Prof. Dr. Gustav Steinhoff: Over the past 15 years, stem cell research has been triggering an enormous progress in developmental biology and Regenerative Medicine. At present, all over the world novel therapies are being developed based on this knowledge. This is clearly trend-setting for the medicine of the 21st century by focusing research and development on regenerative and – with it – healing medicine. In particular, the novel technologies allow us to analyze patient-specific disease mechanisms and to develop personalized diagnostic methods.

What do you deem realistic in stem cell research?
Prof. Dr. Gustav Steinhoff: Therapies with adult stem cells have already been successfully applied in the field of hematology, for treating eye and heart diseases in human beings. Because of the multitude of current developments and clinical studies we can expect novel therapy approaches that may induce healing processes for many other diseases in the next years which have so far been inconceivable. For the best possible quality assurance of novel cell therapies extensive tests in the laboratory as well as in clinical trials are legally required. Quality, safety and efficacy of the therapy approaches can be tested in specially designed University innovation centers, such as the RTC. Only after approval by the national authorities and/or authorization by the European Commission, respectively, will the novel therapies be available for all...
In parallel to the worldwide first Phase III trial “PERFECT” for intramyocardial stem cell therapy, which has been started in 2009 on our initiative together with excellent heart centers in Germany, important scientific parameters have additionally been analyzed for a more specific application of stem cells in the future. In different projects, we investigate in how far conventional therapies can be optimized by combination with stem cells.

Furthermore, we want to find out whether a further improvement of stem cell effects on hearts can be reached by genetic modification of stem cells. We try to generate a method for a safe and efficient gene transfer by using non-viral vectors to improve the regeneration of the diseased heart after application of modified cells. Besides investigations of bone marrow derived-stem cells a further subject deals with the programming of selected cells in defined directions. Prof. Dr. Robert David from our group managed to generate a biological pacemaker by direct cell reprogramming.

What we have so far only been able to show in the пе-тритищ with mouse cells could possibly replace artificial pacemakers in the future.

Your colleague from Essen, Dr. Wolfgang Ingenhag, has called you a “hidden champion”. Are you upset about this?

Prof. Dr. Gustav Steinhoff: No, I rather consider it as a compliment. In 2001 I was the first physician world-wide who injected adult stem cells in the heart. This made Rostock a well-known place in the scientific community and finally resulted in the foundation of the RTC only seven years later. In spite of our rather remote location we have excellent conditions for our research in the Hanseatic city of Rostock. One of our specialties is that the research division of the RTC is affiliated with the University Rostock Medical Center. Therefore, we have the advantage of a close collaboration between our research in the lab and the clinic and patient care. To optimize corresponding procedures we have successfully established a translation management at the RTC.

In addition, we have excellent connections to the industry. The companies Miltenyi-Biotec GmbH and Bio-tronik GmbH have successfully settled in the region, SeraCell Stammzelltechnologie GmbH is a spin-off of the University of Rostock. These regional companies with their focus on stem cell technologies and medical techniques contribute to an enormous added value of the location. Therefore, we are well-positioned for international competition.
Our work aims at understanding the function of selected stem cell populations and the complex mechanism of regeneration in target tissue. Based on this background and by applying mechanistic research approaches, we want to improve the efficacy of regenerative therapies and generate brand-new approaches. Here, we take the conventional line of “Bench to Bedside”, however we also reverse the procedures many times. Based on the results of clinical application, we develop novel research approaches.

At the RTC we work intensively in particular with bone marrow-derived primary stem cells. At the beginning, we have focused on investigations of the subpopulations of CD133+ (hematopoietic stem cells) and CD271+ (mesenchymal stem cells), but in the recent past we have extended our focus on characterization of cardiomyocyte subtypes which has resulted in the successful isolation of Mesp1+ progenitor cells and generation of pacemaker cells by means of stem cell programming.

Hematopoietic bone marrow-derived CD133+ stem cells

In 2001, hematopoietic bone marrow-derived stem cells have first been applied in clinical trials by German heart surgeons and cardiologists. The transplantation of these cells (CD133+ subpopulations or mononuclear cells (MNC)) provided beneficial effects on heart function and of myocardium regeneration in patients with cardiovascular diseases.

From 2011 to 2005 Prof. Steinhoff conducted clinical trials (Phase I/II) (7-11) with autologous bone marrow-derived CD133+ stem cells applied to patients with chronic ischemia after myocardial infarction. This means that the surgeon injected a suspension of isolated and purified cell populations intramyocardially in the infarct border zone during bypass surgery. The stem cell transplantation was well tolerated and showed an improvement of heart pumping function in the verum-group compared to the control group.

Establishment of stem cell isolation and storage techniques

Besides hematopoietic stem cells which express the marker CD133 and CD34, the bone marrow contains cells which are able to generate mesenchymal colonies (so called “colony forming unit-fibroblasts”, CFU-F). Compared to CD133+ stem cells, CD133− stem cells are less differentiated. We found out that all of the CFU-F generating cells are located in a population which expresses the marker CD271. This means that a separation from fresh bone marrow can be conducted with the help of this new marker. According to our results, hematopoietic and mesenchymal progenitor cells are two clearly distinguishable populations. Hence, a subsequent dual isolation method of CD133+ and CD271+ cells from a single bone marrow sample is now possible. With this, we have established isolation techniques which allow us to collect the needed stem cell populations for our further experiments.

The stability of a stem cell product over a certain time is essential for its clinical application because of methodological and organizational reasons resulting from the manufacturing procedure and the transfer from and to the operating room. Stability analyses of CD133+ stem cells revealed that a storage period of maximum 30 hours did not impact the quality and function of the cell product at all. Consequently, impairment of efficacy and safety will not be expected when applied in human beings. However, a storage period of 72 hours caused a significant loss of stem cell function. These results are of importance for the efficacy and safety of a stem cell product in the clinical application (14, 15).

Migration capacity of hematopoietic stem cells

Migration and homing ability of stem cells towards a target tissue are essential features for their efficacy. It is of critical importance that transplanted cells migrate effectively into the surrounding area of damaged tissue.

Pre-clinical knowledge

Prof. Steinhoff’s clinical trials were preceded by publications about non-clinical studies, in vivo and in vitro, whose positive results allowed the application to human beings. Until today the mechanistic knowledge about mode of the heart is still inadequate. In the meantime, it is predominantly assumed that the regenerative efficacy is based on an increase of angiogenesis (formation of new blood vessels) including the paracrine effects which are of fundamental importance.

It has been published in many articles that the CD133+ subpopulation has a key role in angiogenesis (growth of new blood vessels) including regenerative efficacy is based on an increase of angiogenesis including paracrine effects which are of fundamental importance. In particular, the effect was induced by CD133+ stem cells, which are able to reduce apoptosis of cardiomyocytes and to increase the contractility of tissue. From today’s perspective cell differentiation as well as mediator release are involved in these procedures. However, the regulation of these signalling pathways has not yet been analyzed. This shall now be identified by novel mechanistic research approaches.

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**Mesenchymal bone marrow-derived**

**CD271+ stem cells**

Mesenchymal stem cells (MSC) are considered as promising cells for treating diseases associated with damage of heart tissues. Under laboratory conditions, the cells have advantageous features because they can be easily isolated and quickly proliferated ex vivo by adherence to plastic. MSC are generally uncomplicated to isolate. They are rapidly and permanently available in larger amounts from cell culture. These features benefit the therapeutic application. Since the actually used hematopoietic stem cells for therapies at the RTC do not exhibit such beneficial features we are presently working intensively on this human bone marrow-derived subpopulation.

We were able to show that depending on its source, the human MSC exhibited differences in cardiac regeneration potential. Our studies showed that LAD ligation induced MI immune-deficient mice injected with bone marrow-derived MSC (BM-MSC) revealed significantly improved heart function compared to mice injected with umbilical blood-derived MSC (CD-MSC) which were isolated and purified in the same manner. The study also demonstrated that animals treated with BM-MSC showed the highest survival rate. Furthermore, their hearts had a significantly reduced cardiac remodeling (20). This is the reason why we are currently focusing on bone marrow as source for our analysis at the RTC.

**Mode of action**

Today it is assumed that MSC stimulate the production of growth factors and cytokines in cardiac tissue and/or produce itself on-site after transplantation (21). Hence MSC are able to inhibit directly or indirectly inflammation and replace damaged cells as well. Overall, they effect their neighboring area and support the endogenous cardiac repair.

The identification of the underlying mechanism (22) is still a major focus of the RTC.

**Isolation**

Until now, it has been impossible to effectively isolate MSC freshly from bone marrow for their therapeutic application using specific surface markers and their adhesion and differentiation capacity. For the first time, with help of the surface protein CD271, we managed to isolate all mesenchymal progenitor cells of a single population from human bone marrow by means of immuno-magnetic methods. Furthermore, we were able to prove further mesenchymal markers being expressed on freshly isolated CD271+ cells using a multiple staining. This method has been successfully established by us and may lead to the development of new approaches for the development of optimized therapies.

This research program lays the foundation for the development of novel MSC stem cell preparations for the application to human beings to treat cardiovascular diseases. When we have completed our planned pre-clinical work and the standardization of a GMP-conform manufacturing procedure a quality assured and good characterized MSC product will be available for clinical testing of safety and efficacy. Finally, this may result in a primary cell product, in each case freshly prepared by us at the “Point of Care” – if practicable - or it may result in expanded cells which have the advantage to be available in larger amounts and from storage.

Even if it is easy to cultivate MSC, as mentioned above, it will be a long way until it will be possible to use MSC derived from cell cultures in therapy. For this purpose, the cell stability in the cell cultures needs to be proven. This will require intensive investigations of cell growth and expansion as well as a critical evaluation of all used expansion media.

It is known, that uncontrolled expansion of non-purified and long-term cultured MSC cause cell degeneration such that these cells are high-risk for therapeutic application. Likewise, our own previous analysis showed that rat MSC spontaneously transformed early at the passage. Their typical morphological spindle shape changed to a compact shape (23,24). The expanded MSC proliferated abnormally fast and some of them formed themselves to multilayer aggregates. Furthermore, we were able to observe that the number of their chromosomes was unstable. Our immunophenotypic analysis revealed that the characteristic membrane proteins CD29, CD44, CD90 and CD117 are missing on these cells. Experiments with

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These findings led us to the conclusion that the development of primary cell preparations using the CD271+ sub population for the application to human beings exhibits a promising therapeutic potential such that we want to promote its application. It also became clear that currently MSC cell products derived from cell cultures are still high risk for therapeutic application such that substantial further work is needed. We are willing to meet this challenge in the next step.

Cardiovascular Mesp1+ progenitor cells

A further future aim of our group is to program pluripotent cells directly thus that they effectively differentiate to specific cells. For this purpose, we first need to identify the biological processes of cardiovascular stem cell differentiation. In our previous work, we were able to show that the transcription factor Mesp1 is a central regulatory element for the induction of cardiovascularness (27-31). In this context we found the promoter of the Dkk-1 gene to be up-regulated by Mesp1. This up-regulation effects the inhibition of the canonical Wnt signaling pathway. In the following, we were able to manage cardiovascular programing of ES-cells into various different myocardial cell subtypes for the first time: MesP1 lead to early but still multipotent cells whereas Nix2.5 induced the occurrence of terminally differentiated ventricular cells. Most recently, we established the Mesp1 promoter for the isolation of common cardiovascular progenitor cells by means of magnetic cell sorting (MACS).

The next focused steps are meant to continue the characterization of this Mesp1+ positive cell population as well as the identification of Mesp1-dependent signalling cascades, including the characterization of Mesp1 promoter in respect of its regulation by upstream factors and the identification of involved co-factors. For this purpose, we will use our established ES as well as new ES and iPScell lines. Amongst others, we will conduct electrophysiological and pharmacological analysis and try verify of cardiovascularogenic multipotency by means of in vivo analysis. We expect to gain new understanding of yet unknown regulation cascades and factors which are significantly involved in the induction of cardiovascular differentiation processes. In the future, we hope to manage purification of early staged cardiovascular cell types with respect of future clinical application without genetic modifications. For all these experiments we aim at a combination of system-biological approaches with conventional cell biology.


Pacemaker cells

At the RTC, we do not only work on "conventional" heart diseases but also on treatment methods for other types of cardiovascular disease.

The "Sick-Sinus-Syndrome" is used as a collective term to describe a series of diseases of pacemaker cells in the sinus node of the heart. Suitable cell sources for cell replacement are pluripotent stem cells, preferably autologously induced pluripotent stem cells (iPSC). To continue our preliminary work, we used the approach of subtype-specific programming (32) cells into cardiomyocytes ES working with Tbx3, a key factor for induction of sinus nodal cells, in combination with Myh6 promotor-based antibiotic selection. In a recently published work we were able to show for the first time that this method leads to high-purity pacemaker cell aggregates generated from murine ES cells whose functionality could be proven both in vitro and ex vivo (33,34).

The next aim will be the completion of the functional characterization of murine pacemaker cells and the performance of in vivo "Rescue experiments" using a transgenic mouse line. Parallel to this, we will transfer our methodology for application to the generation of human pacemaker cells from iPSCs. Then, RNA-sequencing of murine and human sinus nodal cells will be conducted.

Our goal is to identify new factors and cell surface molecules with which cell programming and purification approaches can be optimized such that clinical translation can be achieved.

34. Schutzrechtmeldung am 20.12.2013 durch die Universität Rostock: DE102013114671.6: "Verfahren zur Erzeugung von Sinusknotenzellen (Herz-Schrittmacher-Zellen) aus Stammzellen"
„I have been working at RTC for 5 years. Here I learned to apply the knowledge gained previously and work in team. Every single day in the RTC lab I use the chance to learn something new and grow up as a researcher.“

Evgeniya Delyagina
Scientist, PhD Student RTC

„Over the course of the past years the collaboration between the RTC and the Saint Petersburg State Chemical Pharmaceutical Academy (SPCPA) has been evolving well. Today, we conduct scientific investigations of the new polymer delivery systems for the supply of various intracellular constructions.“

Prof. Dr. Olga Kudritskaya
Chemisch-Pharmazeutische Akademie (SPCPA)
St. Petersburg, Russland
2. Clinical Implementation

From the very beginning all research and development at the RTC has the strategic goal of clinical implementation. For a successful translation, the RTC team possesses profound expertise in the area of legal and regulatory requirements.
Before that, the first Phase I trial (2001–2003) was conducted in Rostock with which it was possible to proof the safety of intramyocardial stem cell therapy with bone marrow-derived CD133+ stem cells. Subsequently, a randomized Phase II trial (2003–2005) was conducted in which a significant improvement of heart (pumping) function by means of the same stem cell therapy could be demonstrated. In parallel, a randomized placebo-controlled Phase IIb trial was conducted at the German Heart Center, Berlin (2005–2011). Also in the course of this study, bone marrow-derived CD133+ stem cells were used, however, there were differences in the concentration of products, in the way of application and also in the indication in comparison to the previous studies. At this time, it is not clear whether these differences played a role for the fact that no significant difference could be found between the placebo-group and the group that had been treated with stem cell therapy. The outcome of the multicentric Phase II trial PERFECT which aims for the systematic proof of safety and efficacy of this novel therapy may lead to clarification regarding this point (see 35). PERFECT is the first randomized placebo-controlled Phase III trial on CD133+ stem cells, which is strictly conducted according to the rules of GCP (36). Since the study is designed to be double-blind, there are so far no results regarding the efficacy of the therapy. Regarding safety, there have so far been no adverse events which imply a therapy risk. Already in the course of 2014, a partially unblinded interim-analysis is planned from which data regarding the efficacy of the therapy may be expected.

For the first time, this clinical study is accompanied by an extended research program for quality assurance and for research of the basic mechanistic principles (37–38). For the conduct of PERFECT as well as its accompanying research program, the RTC has been able to gather several leading Heart centers in Northern and Eastern Germany in the frame of the “Kompetenzraum kardiale Stammzelltherapie” (Competence liaison cardiac stem cell therapy); these are the Hannover Medical School, the German Heart Center Berlin, the University Heart Center Hamburg, the Heart Center Leipzig, the Heart and Diabetes Center Bad Oeynhausen, and the University Rostock Medical Center. Manufacturer of the investigational medicinal product as well as sponsor of the study is the company Miltenyi Biotec GmbH which is also involved in the accompanying research program. Most of the involved clinical trial sites have been subject to an inspection by the German Competent Authorities in the course of last year. During these inspections, no major issues were identified. The results of the study will be published and will serve as a reference standard for future applications of CD133+ stem cells.

GCP – Clinical trials on human beings according to „Good Clinical Practice“

In 2000, the directions for the application of Good Clinical Practice (GCP) were adopted to German law in the form of the GCP-regulation following the European guideline 2001/20/EG. Since then, each clinical trial involving human beings according to §4 Abs. 23 of the German Medicines Act (AMG) has to make sure that its planning, documentation, and reporting the results needs to be in agreement with the requirements of GCP. This also applies to clinical trials with stem cells – provided these are classified as “Advanced Therapy Medicinal Products” or as “Advanced Therapy Medicinal Products” (ATMP), respectively (39, 40).

Since the bone marrow-derived CD133+ stem cells which are investigated in the study PERFECT with regard to their application to the heart are ATMP and hence fall under the German Medicines Act, the RTC is in close coordination with the sponsor and other clinical trial sites – has made sure that the requirements of the GCP are being followed for all stages of planning, authorization, conduct, and subsequent surveillance. An inspection of PERFECT in summer 2013 by the Federal German Authorities on behalf of the European Union has hence not identified any major issue.

With this “GCP-seal of quality” both the study center and the translation management of the RTC are well positioned to conduct further clinical trials on human beings in the context of novel cell- and gene-therapy approaches as “Investigator Initiated Trials” (IIT) in collaboration with industrial sponsors as “Company Initiated Trials” (CIT) in the context of “Me- dicinal Products” respectively (39, 40). Our practical experience and the clinical results of more than 200 stem cell patients show that quality assurance and management in the scope of stem cell treatment – and consequently standardization – are critical factors. Comparisons concerning efficacy and safety without clear definition of indication and treatment standards are not legitimate. Besides clearly defined indication and diagnosis as well as investiga- tional medicinal product (IMP) concerning cell sort, source material, manufacturing method, cell number, cell concentration, excipient, storage- and transport period etc.) and way of application (intramyocardially: injection volume, number and penetration depth of the injections, puncture areal; intracoronary: applied number and location etc.) have to be clearly defined. The signifi- cance of quality assurance and standardization of the- rapies as well as compliance with GCP are also being stressed by the fact that numerous comparative public- ations cast a shadow of doubt on the value of stem cell therapies in cardiovascular diseases because they demonstrate that results are not sufficiently comparable due to lack of standardization and unification.
The RTC considers the topic of quality assurance and standardization as an important task in the frame of its positioning as a reference centre. Therapy standards that have been developed at the RTC are being discussed with the authorities in the frame of the „Competence liaison“ in order to reach standardization. In consequence, it regularly happens that – besides the normal path from „Bench to Bedside“ - the opposite path has to be taken, i.e. clinical approaches have to be re-evaluated in the laboratory.

The RTC considers it as an additional task to communicate the know-how that has been acquired in clinical practice in the form of presentations, lectures and seminars and to discuss individual approaches with interested parties. A further development of an advisory service for regulatory issues concerning planning, surveillance, and realization of cardiovascular stem cell-based ITs is currently under preparation by our study management.

GLP – Pre-clinical development according to „Good Laboratory Practice“

Bone marrow-derived stem cell preparations for cardiovascular application have been classified as „ATMP“ such that they fall under the German Medicines Act. This implies that all legal requirements for the pre-clinical tests of medicinal products apply. However, the authorities acknowledge that these standard requirements are not automatically applicable because of the unique and very diverse structural and biological properties of ATMP. In this sense, there are so far no uniquely defined requirements, detailed instructions do not yet exist for laboratory experiments or for special animal models (41). This also implies that the quality standards according to GLP have not yet been generally requested. Often, appropriate models and corresponding certified laboratories do not exist, yet.

At the RTC, we work on conducting all significant steps of our pre-clinical development work in compliance with GLP. In close connection with the corresponding authorities, the RTC selects, evaluates and demonstrates if possible parameters and procedures for proving quality and safety of stem cell products. Corresponding laboratories and instruments are qualified at the RTC. Also, the RTC takes care of necessary qualification and test procedures. The RTC staff receives special training for all organisational and experimental processes. In the near future, we plan to conduct all documentation in digital form. This will give the RTC a leading position and will allow to permanently expand the spectrum of tests in an uncomplicated manner.

The GLP-test procedures which the RTC plans to establish in the future are meant to become standards for all further non-clinical investigations in the frame of our therapy development. Also, we plan to offer this service to external parties.


In Germany, the permission is granted by the corresponding authority and may only be denied if the regulations of GMP have not been followed thoroughly.

At the RTC, all therapeutically used stem cell products are manufactured according to the Arzneimittel- und Wirkstoffherstellungsverordnung (AMWV) (German „Pharmaceuticals and Active Agent Manufacturing Ordinance“). This regulation defines the application of GMP-regulations for the manufacturing of medicinal products and active ingredients as well as the application of the GSP (German “Codes of Good Practice“)-regulations which apply to the manufacturing of products of human origin – i.e., in our case to the sampling of raw material (bone marrow donation).

The manufacturing of our stem cell products is currently carried out by our partner Seracell Stammzelltechnologie GmbH who possesses the necessary laboratory facility and permissions after formal purchase order from the RTC. At the moment, this applies to the PERFECT applications which are manufactured for the RTC.
At the RTC, we are also preparing the possibility of manufacturing stem cell products on our own. In the future, we plan to manufacture the stem cell products by means of the „Point-of-Care“-procedure (PoC) in our operation areas. This is deemed very advantageous for suitable cell products: by means of far ranging automation we will be able to shorten the production times and improve the standardization. Since the manufacturing will happen in close proximity and time to the treatment of the patient we will be able to significantly shorten the storage time of cells outside the human body. This should significantly improve the quality of the products. It should also shorten the patient’s residence time in the clinic with corresponding positive effects on cost saving and better compliance of the patient.

In advance, we have evaluated several systems which are available on the market with respect to their suitability for a GMP-conform manufacturing in the operation room area and we have then validated and standardized selected GMP-conform cell isolation and purification methods in close cooperation with our industry partners such that these are on their way to approval by the authorities. Our quality assurance system includes the quality assurance of the products in our own RTC-laboratories as well as under contract with other certified labs of the University Medicine Centre.

As the world-wide first clinical trial site for more than one year the RTC is in the possession of a CliniMACS-Prodigy – System following an intensive joint research with Miltenyi Biotec. This system is a unique novel development for GMP-manufacturing of subpopulations from bone marrow. This closed system which has been developed by our partner Miltenyi Biotec GmbH is a further development of the isolation system CliniMACS which has so far been used for the manufacturing of CD133+-cell products in clean rooms. With support by Miltenyi Biotec, the RTC is validating and standardizing this system for GMP-manufacturing at our facility in the operation room area. As a first step, we plan to apply for manufacturing authorization for PoC-manufacturing of CD133+ stem cells. Later, we also plan to isolate other cell populations for therapeutic applications.

Our application for manufacturing authorization will be submitted to the competent authority of the state M-V (AMÜSt). We will apply for authorization for both: to produce investigational medicinal products (IMP) for clinical studies and to manufacture products for patient care according to §4 b AMG (Hospital Exemption). After achieving the manufacturing authorization, we will produce IMP as PoC for our already planned clinical trials with CD133+ stem cell products. In parallel, we plan to offer stem cell therapies to our patients – as we did before the ATMP-regulation – under the „Hospital Exemption“ for which we also will prepare the stem cells in the „Point-of-Care“-procedure as introduced above. For the therapy we have already been successful to secure reimbursement by the health insurance by means of a DRG.

“RTC not only plays a significant role in stem cell and cardiac therapy worldwide. It is also a wonderful and unique place which maintains the right environment to support young scientists to flourish and grow.”

Nan Ma
Prof. Dr. med. Dr. rer. nat
Institute of chemistry and biochemistry
Free University Berlin
Department Head of Biocompatibility
Helmholtz-Zentrum Geesthacht, Center of biomaterial research, Teltow, Germany

In the operation room of cardiac surgery, we have installed a prototype facility for our own „Point of Care“- manufacturing of stem cell products. In addition, we have installed a quality assurance system, we have taken measures for room- and instrument qualification, and provisions for validation, we have audited our cooperation partners, and we have trained the involved staff. With our application for manufacturing authorization all SOPs and further documents for manufacturing will be finalized such that our manufacturing site may be subject to an inspection by the authorities.
3. Technology developments for stem cell modifications

At the RTC, translation is a permanent process. New insights from basic research as well as the application of novel technologies form the basis for a continuous innovation process.

The aim of this process is both the identification of novel regenerative approaches and the improvement of already existing therapies. At the beginning, there is always the development phase in the laboratory where both in vitro and in vivo tests are performed to ensure quality and safety. Subsequently, clinical trials are conducted to demonstrate safety and efficacy in human beings with the overall goal to achieve market authorization to routinely treat patients with these novel therapies.

We see a large potential for the improvement of the efficacy of stem cell therapies through modification of stem cells by means of gene transfer. For this, we put priority on the application of magnetic nanoparticles in order to avoid hazards associated with viral vectors. Another area of our work is the optimization of cell seeding techniques in the frame of cardiac “Tissue Engineering”. By means of “local drug release” with erythropoietin, we try to optimize the efficiency of such approaches. Further research directions are studies on “VEGF and angiogenesis” and on “AT II receptor stimulation”.

Already now, we frequently discuss our ideas with experts for bioinformatics. On the basis of our data, these colleagues are able to design so called in-silico models. This is nowadays known under the heading “System Medicine”. The results of such in-silico model-investigations are then to be verified by means of in vitro/in vivo –investigations.

Magnetic nanoparticles for non-viral gene transfer

In a previous study, we have been able to demonstrate that in-vitro magnetically controlled gene transfer of a viral MNP/Ad-complex in rat MSC amplifies transduction by as much as a factor of fifty. Rats who received an injection of a MNP/AdhVEGF-Complex through their tail vein which was subsequently guided towards the heart by means of a magnet which had been placed in the infarct zone revealed a significantly enhanced VEGF-expression in the ischemic part of the heart (42). Four weeks after the infarction, this lead to a significant improvement of the heart function and to a reduced chronic cardiac remodeling. This implies that magnetically controlled gene transfer opens the possibility for a targeted local therapy in the frame of a systemic application. In general, future clinical applications should aim to avoid viral gene vectors because of their potential side effects.

Even without application of an external magnetic field, the combination of MNP with a complex composed of PEI and plasmid-DNA (pDNA) resulted in enhanced transfection efficiency in MSC. Using confocal microscopy, we were able to show that pDNA is being released by the MNP in the perinuclear zone and then enters the cell nucleus. This experiment revealed that the MNP resulted in an enhanced pDNA release rate and that the enhanced transfection efficiency of the pDNA/PEI-complex prevailed for up to 48 hours after transfection.
miRNA in stem cell differentiation.

It is well known that miRNAs play a major role in stem cell differentiation as post-transcriptional modulators of gene expression. In our investigations, we were able to demonstrate a close relationship between functional changes of stem cells in cell culture under hypoxic conditions and a significant change of global gene expression profiles (48). In order to clarify the role of miRNA in the differentiation of human stem cells, we initially modified the activity of selected miRNAs in stem cells after which we evaluated the corresponding effect. It had already been documented in the literature that miRNA-126 promotes angiogenesis. In our in vitro angiogenesis-test system we were subsequently able to show that the enhanced expression of miRNA-126 amplifies network formation.

In order to utilize the large potential of antisense RNAs in the future, we have furthermore extended our non-viral DNA-transfer techniques by the transfer of miRNA to stem cells (49, 50). Currently, we are planning further activities in this area.

Figure 7: Processing of transfected pre-miRNA via magnetic nanoparticle complexes (miR/PEI/MNP). Confocal laser scan microscopic analysis of miRNA (miR-335) 72 hours after transfection of human mesenchymal stem cells.

Another method which is currently exploited at the RTC is a novel “three-channel airbrush technique” (Vivostat-Co-Delivery-Airbrush-System). This airbrush system has been chosen to find out whether it is possible to realize intraoperative heart valve Tissue Engineering by means of a stem cell-plus-fibrin composite. With the airbrush system we sprayed a complex consisting of human CD133+ stem cells and fibrin on xenogenic pulmonary valves from pig. In a bioreactor, the cells were able to survive under physiological pressure-flow-conditions for 96 hours. During this period, the inner sides of the transplants showed the generation of adherent spindle-shaped CD133+ stem cells hinting at the differentiation of CD133+ stem cells in the complex under flow conditions.

Comparative investigations with the "LIFT" method and the "Three-channel-airbrush technique" for cell seeding of artificial heart valve leaflets with MSC and HUVEC in fibrin reveal differences with respect to their positioning on the cells on the substrate and with respect to their effectiveivity.
Erythropoietin as a regenerative active ingredient for the heart

Erythropoietin (EPO) is a glycoprotein with cytoprotective and regenerative properties. In a rat model, we have investigated the local effect of a single intramyocardial injection of EPO (3000 UI/kg) after myocardial infarct (MI). After the EPO injection, we were able to observe a reduction of infarct size, an inhibition of reperfusion injury, and an improved cardiac function. In addition, our study revealed an accelerated intra-cardiac cell proliferation. Also, we were able to show a significant upregulation of the stem cell homing factor SDF1 (stromal cell-derived factor 1) and an improved recruitment of CD117+ and CD34+ stem cells (56).

In the ischemically damaged myocardium we were able to observe an intracardial induction of cyclin D1 and Cdc2 (Cell-division-cycle-2-kinase) for which it is known that they foster the cell cycle (54). Both factors play an important role in endothelial proliferation and in the genesis of mature vessel structures. In a model of spinal cord ischemia, we identified SDF1 and angiogenesis as an important approach for improving the efficacy of regenerative therapies and we will consequently continue corresponding investigations in the future.

Hence, EPO is of great interest for the regeneration processes of the heart that we are currently investigating. For this reason, EPO application appears to be an important approach for improving the efficacy of regenerative therapies and we will consequently continue corresponding investigations in the future.

SDF1 and angiogenesis

We have developed technological approaches on the basis of gene therapy and matrix molecules for enhancing the migration of stem cells into the myocardium. Non-viral gene therapy approaches proved to be successful and revealed an enhanced migration of bone marrow-derived CD117+ cells into the myocardium as well as an enhanced angiogenesis (56, 57). Similar results were also achieved with Matrigel-application (58). Based on these studies, we are currently working on the mechanism-specific application of various regenerative active ingredients.


AT2-receptor stimulation

The cardiac stem cell-mediated therapy has a large potential for the treatment of cardiac diseases. At the RTC we work on the identification of ways to improve the therapeutic efficacy of intramyocardially applied bone marrow-derived stem cells for the myocardial regeneration. In this frame, we have also been working on Angiotensin II (59-61).

Angiotensin II, the main effector of the renin-angiotensin-system, hampers the cardiac regeneration process by means of its receptor molecules ATR1 and ATR2. In previous studies, we were able to demonstrate a post-infarct expression of the AT2-receptor in cardiac c-kit+-progenitor cells. This insight gave us the possibility to improve the cardiac regeneration process by means of AT2-receptor modulation. In addition, we have recently succeeded to demonstrate an improved therapeutic efficacy of bone marrow-derived progenitor cells after pre-conditioning with AT2-receptor stimulation in a rodent model.

Based on these initial successes, we now intend to develop translational and clinically relevant approaches for AT2-R-mediated cardiac regeneration. We suspect that an effective AT2-R-progenitor cell-mediated cardiac repair is based on molecular/cellular mechanisms which have so far not been identified. These bone marrow-derived AT2-R-progenitor cells should be seen as a so far uncharacterized sub-population and are currently being intensively studied in our laboratories.


4. Facts and figures

Strategy and Structure

The Reference- and Translation Center for Cardiac Stem Cell Therapy (RTC) at Rostock University combines the research-intensive parts of the Clinic for Cardiac Surgery and the Research Laboratories of Cardiac Tissue and Organ Regeneration at Rostock University and coordinates their collaboration. The RTC is headed by Prof. Gustav Steinhoff and also comprises a dedicated translation management. It is located at the Biomedical Research Center (BMFZ) at Rostock University. The RTC is organized to efficiently handle the entire complex process of medicinal product development, its application in human beings and its tracking:

- The R&D-center focuses on the generation of new findings by means of basic research. These new insights are then applied in the frame of the pre-/non-clinical development in order to develop new quality-assured products by means of standardized technologies and by animal model studies which are conducted following „Good Laboratory Practice (GLP)“. In addition, the R&D-center reviews, validates and develops new manufacturing procedures and it also conducts certain service tasks such as the release of products according to „Good Manufacturing Practice (GMP)“.

- In our Clinical Center, we test the safety and efficacy of the new regenerative products in human beings. These studies are conducted in compliance with legal schemes (Phase I – III) and in accordance with the regulations of „Good Clinical Practice (GCP)“. Following approval by the legal authorities the authorized stem cell products are used for patient treatment. The health condition of all these patients is subsequently monitored for the rest of their lifetime via the RTC-register in order to evaluate the long-term-safety and efficacy of the therapy as required by the regulations of „Good Vigilance Practice (GVP)“. Furthermore, the RTC itself manufactures those stem cell products for which it has received official authorization for in-house production (as „Point of Care“-manufacturing) according to „Good Manufacturing Practice (GMP)“. This work is carried out in the surgery department of the Clinical Center by specially trained personnel which is being recruited from staff of the clinic and the laboratory.

- It is the task of the translation management of the RTC to act as a link between the R&D- and the Clinical Center in order to make sure that the strategic goal of all staff members remains the therapeutic goal of the „Regrowing Heart“. Accordingly, the procedures for translation need to be permanently adjusted and optimized in order to position the RTC as a reference center. Along this way, networking with other centers, cooperation with industry and other groups, as well as the acquisition of necessary third party funds are high priorities. In addition, a decisive prerequisite for the success of the RTC is the knowledge and experience in the area of legal and regulatory requirements. In particular, it is the responsibility of the translation team and its corresponding leading experts to take appropriate steps of quality assurance in close contact with the responsible authorities. This includes the need to make all staff members familiar with and adhere to the regulations of „Good Work Practices (GxP)“. In particular, it is the translation team’s task to take all necessary administrative steps for the preparation of clinical trials, including the request for legal permission from the authorities as well as the study management during the course of „Investigator Initiated Trials (IITs)“. Also the team communicates with the corresponding health insurances and makes sure that the expenses for the treatments are reimbursed. Finally, the translation team is in charge of PR activities and supports the promotion of the new therapies.

The Executive Committee of the RTC consists of the initiator of the RTC, Prof. Gustav Steinhoff, and the heads of the three structural units of the RTC as shown in the organization chart below. This ensures the close communication between all structural units and hence makes sure that the overall RTC functions as efficient- ly as possible. The Executive Committee is currently further strengthened by a guest professor who teaches cardiology at the RTC and is bringing in experience from both clinic and science. Administrative matters of the RTC are handled by a project assistant. Also, from early on, the RTC called in an advisory board with whom the RTC strategy is discussed and defined.

The organizational chart below illustrates the structure of the RTC and also lists the number of staff members in each unit. More details on each unit can be found below.
Seven years of successful work
The successful work of the RTC is based on a highly motivated team consisting of scientists, medical doctors, technicians and additional experts. Being part of a University, it is as expected that many young students of Biology and Medical Biotechnology made significant contributions in the frame of the Bachelor’s and Master’s theses: in all, seven Bachelor’s and six Master’s theses have been completed at the RTC since its foundation. Also, work at the RTC contributed to a total of 16 doctoral theses (12 in medicine and four in natural science), and more are currently under preparation. More to that, a total of four habilitation theses (Habilitation Qualification for German Professorship) were completed in the years 2010 – 2012, comprising two such theses in medicine and two in natural science. Remarkably, a total of 101 peer reviewed papers have been published in the period from 2008 to the middle of 2014 with an impact factor of 3.17 on total.

In 2012, three RTC scientists were appointed as professor (Professorship) were completed in the years 2010 – 2012, comprising two such theses in medicine and two in natural science. Remarkably, a total of 101 peer reviewed papers have been published in the period from 2008 to the middle of 2014 with an impact factor of 3.17 on total.

In 2012, three RTC scientists were appointed as professors at other Universities, namely at Berlin, Ulm and Shanghai. In the same year, the RTC was able to fill a newly formed professorship for “Regenerative Medicine in Cardiac Surgery” at the Rostock University. In addition, five younger investigators received awards for their work at the RTC. In 2011, the RTC was named a “Landmark in a Land of Ideas”, and in 2013 the RTC received the award for „Collaborative Research“ of the Rostock University.

Under the overall direction of Prof. Dr. med. Gustav Steinhoff, this service-activities were headed by Prof. Dr. rer. nat. Nan Ma, who was in charge of that already before the RTC was founded. In 2013, she was appointed as professor at the Free University of Berlin in recognition of her excellent work on migration and differentiation potential, angiogenetic effects and interaction of stem cells with host tissues. As her successor at the RTC, Prof. Dr. rer. nat. Robert David was appointed as head of the R&D-unit in 2013. His research area is the characterization of key factors in stem cells as well as the programming of cells as specific cells, such as pacemaker cells of the heart. From 2009 until 2014, Prof. Dr. B. E. Strauer stayed at the RTC as a guest professor. Being a very experienced cardiologist and scientist, his advice during the installation of the RTC and its academic positioning phase has been highly appreciated.

Since 2008, the Clinical Center at the RTC has been led by Priv. Doz. Dr. med. Alexander Kaminski, who completed his habilitation at the RTC in 2011. Already from the beginning he received invaluable support from Sandra Babinski, who significantly contributed to the fact that the RTC after the successfully completed inspection by the Competent Authorities can benefit from the “GCP-Quality Seal”.

Thanks to the profound knowledge and industrial experience of Dr. rer. nat. Guudrun Tiedemann as well as her familiarity with statutory and regulatory requirements, the RTC has been able to establish a translation management of high professionalism. Under her leadership, several teams of young scientists contributed to the joint effort of establishing procedures of quality assurance and standardization for the development, production, and application of novel therapies to ensure safety of and benefit for our patients of the RTC.

The work of the RTC has been closely followed by its scientific advisory board in which experts from various fields have been gathered. More than once, the advisory board provided invaluable advice to the executive committee in cases of problems with translational procedures.

Infrastructure
- The total laboratory space available to the BMFZ amounts to 256 square meters plus additional office space of 44 square meters.
- For in vitro experiments, the RTC has access to laboratories with safety levels S1 and S2. In addition, already existing laboratories were qualified to comply with GLP requirements.
- Maintenance animals and experimental investigations including animals are conducted in the rooms of the neighbor Institute for Experimental Surgery of the University Medicine of Rostock. There, we also have access to rooms which have been qualified according to GLP regulations.
- The laboratories are well equipped for molecular-biological (programming/differentiation) and cell-biological studies (cell culture, cell staining, cell isolation/sorting, stem cell characterization, functional analysis) as well as for Tissue Engineering. Also, specific areas are reserved for gene-technological work (e.g., (non-) viral transfection).
- Concerning large equipment for analyses, we have access to a FACS LSR 2 from Becton-Dickinson (high-end version with four lasers) for stem cell diagnostics; also there a FACS-sorter (BD) and various MACS-sorters (Miltenyi Biotec) for cell sorting. For microscopic studies, we use various different systems including a super-resolution confocal Laserscan Microscope System „Elyra PS1“ for live cell imaging as a high end device.
- At the RTC, cardiovascular in vivo experiments are conducted with small animal models (mice, rats). Experiments with larger animals are conducted at partner laboratories. Our high quality cardiac functional diagnostics comprises animal-telemetric investigations by means of long term ECG and echocardiography, heart catheter functional diagnostics with pressure-volume-loop, exercise tests, as well as imaging methods for cardiac functional measurements (small animal PET-CT).
- The Clinic for Cardiac Surgery – which is at a distance of 100 m on the other side of the street from the RTC labs – hosts the RTC study center for the conduct of GCP-compliant trials. By intention, these offices are located close to the clinic in order to allow for a close and optimal interaction between the clinical trial investigators and study assistance involved in clinical studies with the nursing staff being in charge of the patients.
- Within the operating room area of the Clinic for Cardiac Surgery, we established a prototype manufacturing site for our own point of care manufacturing of stem cell products. Different cell isolation and purification methods have been validated and standardized according to GMP by the RTC and its industry partners in preparation for manufacturing authorization. The quality assurance of the in-house manufactured products is taken care of by the RTC-laboratories as well as under contract by certified laboratories of the University Medicine.
- For a quality assured and standardized application of stem cell products, new procedures are permanently developed and evaluated; also existing procedures are permanently optimized.
- The translation management paves the way for „Bench to Bedside“ (and back) and makes sure that all work is conducted in accordance with legal and regulatory requirements (GxP).
- Much effort has also been spent on intensive PR activities.
- Finally, the RTC is fully integrated into the curriculum of the University Rostock Medical Center by means of lectures, seminars and practical courses.
Our team
Under the overall direction of Prof. Gustav Steinhoff, Dr. Gudrun Tiedemann heads the translation management and has the position of an acting manager, PD. Dr. Alexander Kaminski heads the Clinical Center (all since the foundation of the RTC), and Prof. Robert David is in charge of the R&D-Center (starting in 2013). This executive committee is being supported by the assistants Jana Gabriel and Katrin Höfer.

At this moment, the following natural scientists are employed at the RTC as research associates: Dr. Ralf Gäbel, Dr. Jana Große, Dr. Sandra Kurzawski, Dr. Cornelia Lux, Dr. Christian Rimmbach, Dr. Ulrike Ruch, Dr. Frauke Stähler and Dr. Hoang Tu-Rapp. In addition, a total of 14 additional young scientists are currently working at the RTC who are heading for the completion of their doctoral theses. Additional laboratory support is currently provided by Madeleine Bartsch, Margit Fritsche, Marten Möller and Anita Tölk.

Besides the members of the executive committee a total of nine clinical trial investigators work at the Clinic for Cardiac Surgery who have acquired a certification according to GCP-regulations. Among these, Dr. Peter Donndorf, Dr. Christian Klopsch and Dr. Catharina Neßelmann are currently particularly active in the clinical trial of stem cell therapy and are in the process of distinguishing themselves scientifically in the area of stem cell therapy. This team of clinical trial investigators is being supported by four cardio-technicians and a nursing staff comprising 20 persons. The study office has been headed by the study assistant Sandra Bubritzki since the foundation of the RTC. Additional staff members are currently Dr. Annett Klinder and Petra Paschen.

The RTC is closely collaborating with the Institute for Biostatistics and Informatics in Medicine at the Rostock University in the frame of clinical studies as well in the frame of the accompanying research. In particular, we are happy to count Prof. Dr. Ing. Günther Kundt, Anne Glass and Frank Thiessen as members of our team. Already since 2008, we have been collaborating with the company Miltenyi Biotec (Sponsor) as well as five additional German Heart Centers (Sites) in the frame of the study PERFECT which is scientifically being led by Prof. Gustav Steinhoff (LKP). We surely consider the clinical trial investigators and study nurses from these centers as well as the staff members from the sponsoring company who are involved in this study as members of our team. The same is true for the staff members of the centers Berlin and Hannover who are involved in the PERFECT accompanying research program.

Scientific Advisory Board

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<th>Name</th>
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<td>Prof. Dr. med. Dr. iur.</td>
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<td>Frank Emmrich</td>
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<td>Wolfgang Ingenhag</td>
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<td>Prof. Dr. med.</td>
<td>Christa Schröder</td>
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<td>Prof. Dr. med.</td>
<td>Hans-Dieter Volk</td>
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Name Institute
Charité Center for Health and Human Sciences Berlin, Advocate (Dierks+Bohle, Berlin)
Fraunhofer Institute for Cell Therapy and Immunology (IZI), Translational Center for Regenerative Medicine Leipzig (TRM)
Institute of General Medicine, University of Duisburg-Essen
Albstadt-Sigmaringen Applied Science University
Institute for Medical Immunology (MI), Charité Berlin, Berlin-Brandenburg Center for Regenerative Therapies (BCRT)

Habilitations

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Doctoral theses

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<td>2008</td>
<td>Jan-Anne Lauffs, Cornelius Kasch, Peter Donndorf, Catharina Neßelmann</td>
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<td>2009</td>
<td>Christian Klopsch</td>
<td>Dario Furlani</td>
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<td>2010</td>
<td>Jana Oldigs, Susanna Freier, Christine Teichert</td>
<td>Stephanie Nemati</td>
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<td>Gregor Feldmeier</td>
<td>Wei Wei Wang</td>
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<td>Ingeborg Westien</td>
<td>Ralf Gäbel</td>
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<td>2013</td>
<td>USENI Dritan</td>
<td>Yue Zhang</td>
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Master’s and Diploma theses

Publications

During the past seven years, a total of 101 peer-reviewed papers with an average impact factor of 3.17 have been published by staff members of the RTC. www.cardiac-stemcell-therapy.com/publikationen.php

Awards and Honors

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The most important of these events are as follows:

- In the course of the 3rd EACTS Meeting on Cardiac and Pulmonary Regeneration, which was initiated by Prof. Gustav Steinhoff and subsequently held in Berlin in December 2012, about 90 scientists and clinical physicians discussed new possibilities for the treatment of heart and lung diseases with tissue loss and severe organ damage. During the meeting, special attention was paid to the application of new technologies like nano-technology, stem cell therapy, and gene therapy.

- Jointly with the Clinic for Cardiac Surgery at the Ludwig-Maximilians University Munich (LMU) the RTC initiated a series of “Island Workshops” on the subject “Cardiac stem cell therapy and Tissue Engineering” which particularly addresses young scientists. In 2010 the first workshop was organized by LMU and took place at the Chiemsee. In 2011 the second workshop was organized by the RTC and took place on the island Vilm in close vicinity to the island Rügen. This series has been continued ever since.

- Following an initiative of the RTC the XXXIX International Congress of the European Society of Artificial Organs (ESAO) was held in Rostock in autumn 2012. The congress was chaired by Prof. Gustav Steinhoff who – together with the liver specialists Prof. Dr. Steffen Mitzner and Dr. Wolfgang Ramelow – had invited the community under the motto “From substitution to regeneration, from research to clinic”. The subject “regeneration as a bridge from organ substitution to regrowing organs” was very well received such that more than 600 national and international experts participated in the event.

- The RTC has regularly participated in the annual “Long Night of Science” in Rostock. During these events we offer our laboratories for those parts of the public who wish to learn more about stem cells and their applications for the public in which our research is presented on a popular science level.

- The RTC organized the “Heart Days 2013”. This event was initiated by Prof. Gustav Steinhoff together with colleagues from the University Heart Center in collaboration with the German Heart Foundation and the OSTSEE-Zeitung (i.e., the leading local newspaper). This year, the “Heart Days” took place in the lecture halls of the University Rostock Medical Center over a total of two days. More than 450 patients and other interested people took the chance to obtain first-hand information in the frame of various short presentations and Q&A-sessions on the subject “The weak Heart”.

- Also the “Patient’s Days” organized by the RTC at the BFMZ since 2008 were very well received. The possibility to directly talk to physicians and RTC-staff members surely contributes to our effort to establish close ties to our patients and thereby supports our efforts with respect to the issues of health care research and vigilance. During the “Patient’s Day 2011”, there was one particularly noteworthy specialty that the RTC was able to offer: during that event, more than 400 interested visitors took the chance to have a look at a walk-in model of the heart. At the model, the visitors had the possibility to directly talk to physicians and other RTC staff members and ask their individual questions. In addition, several popular scientific presentations on stem cell therapies of the heart were offered.

- The RTC has regularly participated in the annual „Long Night of Science” in Rostock. During these events we open our laboratories for those parts of the public who wish to learn more about stem cells and their applica-
When talking about the potential of cardiac stem cell therapy for the therapy development in Germany, the RTC in Rostock never remains unmentioned. By means of the widely noticed Phase III trial under the lead of Professor Steinhoff, the RTC has managed to attract national and international attention to a very promising novel therapy.

Prof. Dr. Frank Emmrich
Direktor Translation Center for Regenerative Medicine (TRM) at Leipzig University
Our research partners
Toronto, New York, Stanford, Houston, Tianjin, Beijing, Shanghai, Kobe, Curitiba, Milan, Verona, Lucerne, Vienna, Helsinki, Stockholm, St. Petersburg, Bucharest, Munich, Hanover, Berlin, Leipzig, Bad Oeynhausen, Hamburg, Bergisch Gladbach

Investors
Bundesministerium für Bildung und Forschung
DFG Deutsche Forschungsgemeinschaft
EuropaVemeinschaft
Universitätsmedizin Rostock
Universität Rostock
Landesförderinstitut Mecklenburg-Vorpommern
VDI
PTJ