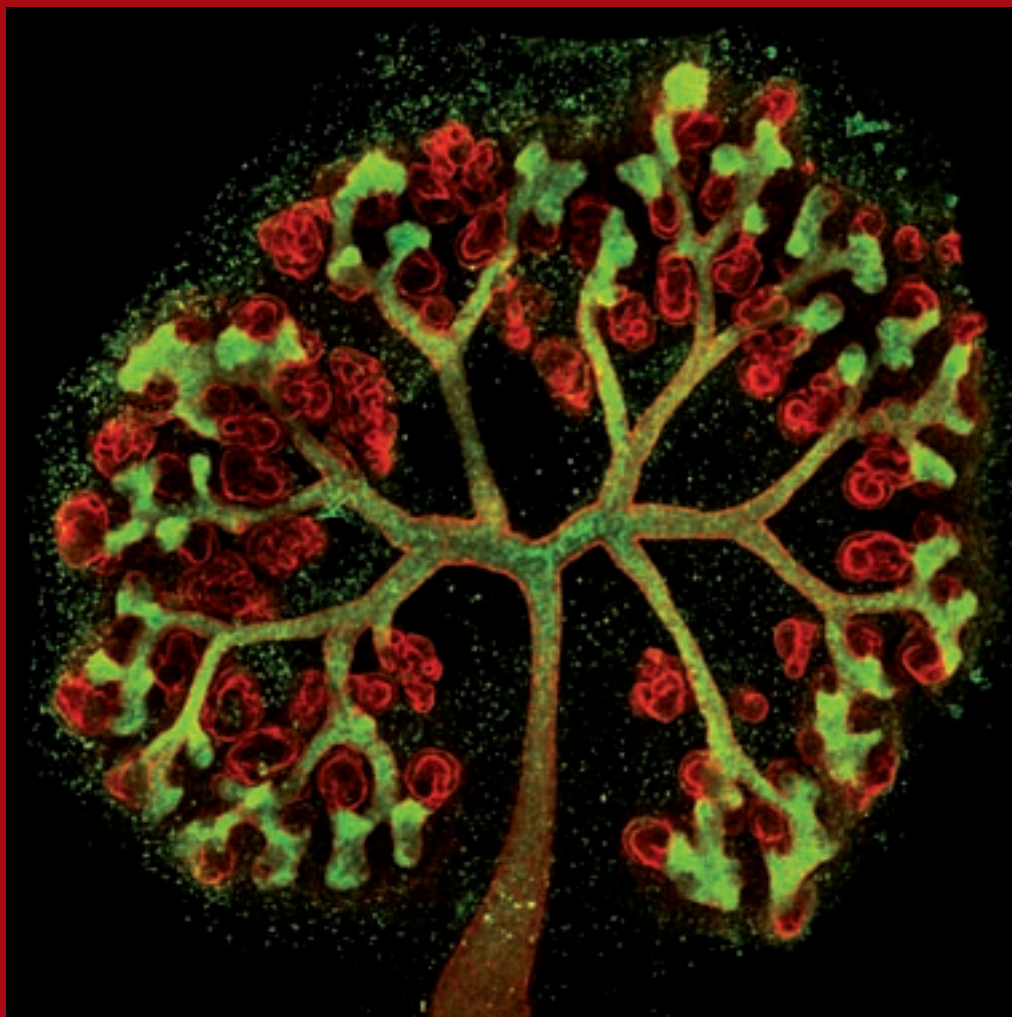


# Regenerative Medicine in Germany



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Brunnenstraße 128  
13355 Berlin  
Germany

Editorial staff:  
Sandra Wirsching  
Dr. Philipp Graf

Design  
Oliver-Sven Reblin

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# Introduction

Regenerative medicine is an emerging interdisciplinary field of research and clinical applications focused on the repair, replacement or regeneration of cells, tissues or organs to restore or establish normal function. Regeneration technologies hold the promise of new and innovative solutions that could directly benefit a huge number of patients. This vision builds on medical breakthroughs that are anticipated for the foreseeable future, that will enable to regenerate previously irreparable tissue or organ function lost due to age, disease, damage or congenital defects.

With approximately 27,000 employees working on biotechnology-related issues across over 700 research institutions, Germany can enjoy a strong international reputation in the field. These facilities are equipped with a combined budget of 2.8 billion euros, of which around 1.1 billion is third party funding. The scientific publications from many of these research institutions are rated extremely highly abroad, and Germany's researchers in the area have attained a high degree of international recognition, including being awarded with the Nobel Prize (Harald zur Hausen, Christiane Nüsslein-Volhard, Erwin Neher). Aided by government funding initiatives, the significance of regenerative medicine and stem cell research within German biotechnological research has risen steadily in recent decades.



# Main Research Infrastructure

Researchers are working on important issues in regenerative medicine in many of the over 100 universities and 180 universities of applied sciences in Germany. Moreover, non-academic research institutions belonging to research organizations (the Max Planck Society, the Gottfried Wilhelm Leibniz Scientific Association, the Helmholtz Association of German Research Centers, the Fraunhofer Society) provide an important institutional foundation for German research in regenerative medicine. The regional distribution of the key research institutes is shown on the map (see figure left).

Content-wise, the field of regenerative medicine in Germany takes in the whole spectrum of technologies and disciplines. This includes research not only into adult, embryonic and other pluripotent stem cells and their cellular differentiation, tissue engineering, biomaterials, bioactive molecules and transplantation/transfusion medicine, but also process-related aspects such as cell isolation, cell cultures, and bioreactors. German research has a broad base also within the fields of application of regenerative medicine, covering the full range of possible indications:

- Skin
- Musculoskeletal system (bone, cartilage, tendons, ligaments, muscles)
- Cardiovascular system (heart, blood vessels)
- Nervous system (central, peripheral nervous system)
- Cellular system (hematopoiesis, immune system, thymus, lymph glands)
- Gastro-intestinal system (liver, esophagus, bile ducts, small intestine)
- Dental and periodontal system
- Respiratory tract (lungs, trachea)
- Endocrinology and metabolism (pancreas, parathyroid gland)

Since 1990, a variety of funding initiatives of the German Ministry of Education and Research (BMBF) have aided the development of an internationally competitive infrastructure in basic and applied research in regenerative medicine. And since 2006, numerous translation centers focused specifically on advanced therapeutic approaches in regenerative medicine have been created across Germany.

### **Center for Regenerative Therapies Dresden**

#### **Goal and Budget**

The CRTD Cluster of Excellence, coordinated by the Technical University (TU) Dresden, was founded in 2006. The cluster is dedicated to interdisciplinary research between nanotechnology, material sciences, medicine, and biological basic research. Using model organisms, the researchers are aiming to explore the critical mechanisms controlled by stem cells in their various developmental stages (activation, proliferation, homing and differentiation). Since 2006, the German Research Foundation (DFG) has funded the CRTD with an annual income of 6.5 million euros. Moreover, a further 2.2 million euros is put aside annually for projects related to stem cell research. (Collaborative Research Centre 655)





Therapies based on cell transplantation with hematological stem cells are already being performed at the CRTD. However, regenerative therapies have not yet been developed for many human diseases such as diabetes, Morbus Parkinson, Alzheimer's, bone/cartilage defects, or cardiovascular diseases. To develop such therapies, the CRTD is exploring mechanisms of stem cell physiology *in vitro* as well as *in vivo* using animal models such as mouse, axolotl and zebrafish. The acquired knowledge will lay the groundwork for an exploration of how newly discovered factors and novel mechanisms could be used for therapies. For this purpose, preclinical and clinical studies are performed. The CRTD also focuses on establishing protocols to manipulate various stem cells, and to integrate these into tissue and organs. In addition, CRTD groups optimize the integration of biomaterials and cells to generate a new generation of living transplants, and develop new concepts to suppress immunological rejection of allogeneic transplants or cells. The CRTD is researching in the following major disciplines: medicine, cell biology, developmental biology, biomaterials, nanotechnology and engineering. Within these disciplines, the research in the CRTD focuses on five research areas: hematology/immunology, diabetes, neurodegeneration/degeneration of the retina, hard tissue replacement, and cardiovascular diseases.

## Research Interests

Also in the cluster alongside a number of institutes of the TU Dresden are the Max Planck Institute for Molecular Cell Biology and Genetics, the Fraunhofer Institute for Ceramic Technologies, the Leibniz Institute of Polymer Research, the Research Center Dresden Rossendorf, the Max Bergmann Center of Biomaterials, the clinics of the University Hospital Carl Gustav Carus, and the Medical Theoretical Center. 18 companies presently support the CRTD network, which currently consists of a core institute of 17 research groups.

## Participating Research Institutes

Furthermore, the Dresden International Graduate School for Biomedicine and Bioengineering (DIGS-BB) in joint association with the International Max Planck Research School for Molecular Cell Biology and Bioengineering (IMPRS-MCBB), representing a faculty of more than 70 group leaders, offers International PhD Programmes that provide outstanding opportunities for university graduates to work towards a PhD or MD/PhD with ambitious thesis projects in the research areas molecular cell and developmental biology, regenerative medicine and nanobiotechnology, biophysics and bioengineering.

## Graduate School

More information: [www.crt-dresden.de](http://www.crt-dresden.de)

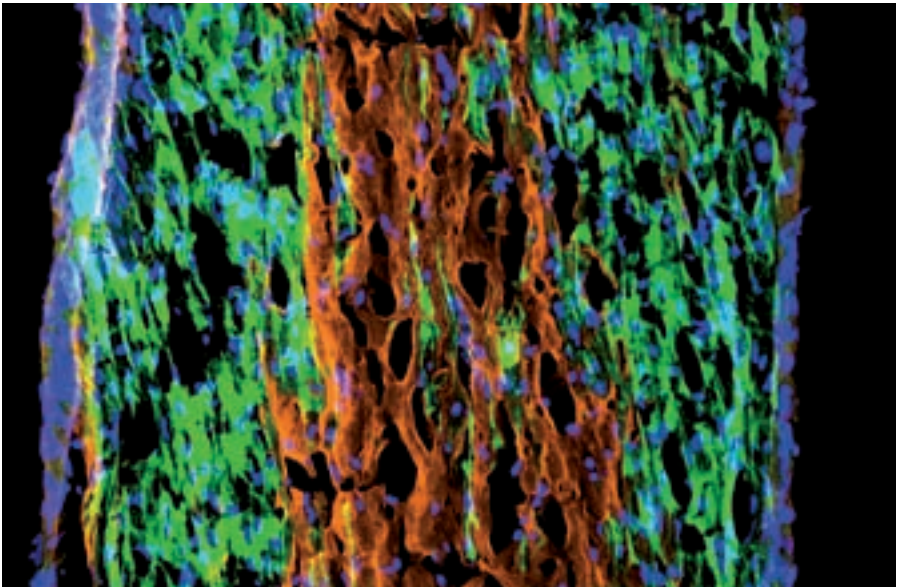
### REBIRTH Cluster of Excellence Hannover

#### Goal and Budget

The Cluster of Excellence “From Regenerative Biology to Reconstruction” (REBIRTH) coordinated by the Medical School Hannover (MHH) was established in 2006. The cluster works in the areas of blood, lung, liver and heart, and is focused on the study of cellular- and molecular structures, as well as signalling pathways responsible for natural regeneration – in individual cells up to entire organs. The center is supported by the German Research Foundation (DFG), which provides annual funding of 6.5 million euros for REBIRTH. The 13.5 million-euro construction costs of the new Hans Borst Center for Heart and Stem Cell Research (HBZ) were financed exclusively by private resources from the Braukmann-Wittenberg Foundation.

#### Research Interests

Researchers working in 40 different teams at REBIRTH study both intrinsic pathways and milieu-dependent mechanisms that control epigenetic reprogramming, cell expansion, differentiation, migration, organogenesis, and disease-specific regeneration. Driven by these insights, they test new approaches for regenerative therapies using novel (if possible somatic) cell sources, which are engineered by applying genetic, epigenetic, as well as scaffold-based principles. Research and development is supported by expertise in various fields of



engineering, chemistry, biophotonics and nanotechnology. Towards patient-focused, applied studies, the existing wide range of certified/ accredited facilities for Good Practice (laboratory, manufacturing and clinical) and close industrial collaborations is being constantly expanded. Upscaling technologies and pro-active biosafety assessment complete REBIRTH's translational activities. Research is focused on disorders of blood (including immunity), heart, lung (respiratory tract) and liver.

In addition to the MHH, seven research institutions are involved in the REBIRTH cluster of excellence: the Hannover School of Veterinary Medicine, the University of Hannover, the Helmholtz Center for Infection Research in Braunschweig, the Fraunhofer Institute of Toxicology and Experimental Medicine (ITEM) in Hannover, the Institute for Animal Breeding Mariensee (FLI), and the Max Planck Institute for Molecular Biomedicine in Münster. In 2008, the Hans Borst Center for Heart and Stem Cell Research (HBZ) was also established.

Participating  
Research Institutes

As a part of REBIRTH, the PhD programme "Regenerative Sciences" started in October 2007. The interdisciplinary programme integrates all scientific and technological disciplines that are relevant for regenerative medicine. At the same time, the PhD programme Regenerative Sciences is integrated in the Graduate School of Excellence HBRS – Hannover Biomedical Research School. Each year up to 20 students from all over the world are accepted into the programme.

PhD Programme

More information: [www.rebirth-hannover.de](http://www.rebirth-hannover.de)

### **Translational Center for Regenerative Medicine Leipzig**

The TRM in Leipzig, jointly funded by the BMBF and the state of Saxony, was founded in late 2006. Here too, scientists from a wide variety of organizations and companies are working together to develop new diagnostic and therapeutic approaches for regenerative medicine, and to transfer these in a target-oriented manner into clinical practice. Financially, the BMBF and the state of Saxony make available 20 million euros.

Goal and Budget

Content-wise, the center is occupied with four areas: Tissue Engineering and Materials Science (TEMAT), Cell Therapies for Repair and Replacement (CELLT), Regulatory Molecules and Delivery Systems (REMOD), Imaging, Modeling, and Monitoring of Regeneration (IMONIT). All the areas of (stem cell-) research are being addressed at

Research Interests

the center, from bioengineering up to clinical application. The research areas of the TRM are supported by three core units, providing specialist support in techniques and procedures related to the efficient translation of basic research through pre-clinical studies and into clinical application: the Computational Microscopy Core Unit (CMCU), the Quality Management Core Unit (QMCU), the Microsurgery and Animal Models Core Unit (MACU).

Translation:  
Therapy-oriented  
Gateway Research

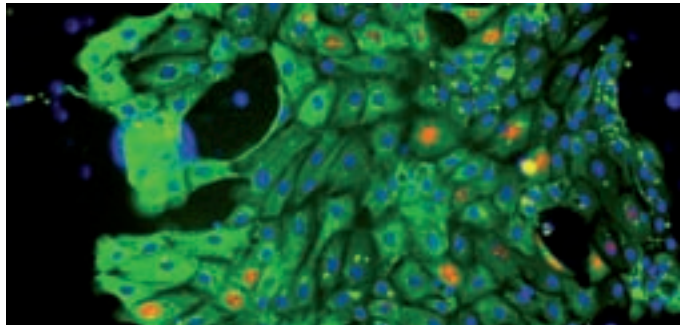
To assure the effective implementation of therapy-oriented gateway research, an award system in which three main gates (G1–3) are conceived has been developed. These gates outline a goal-oriented, milestone approach with each gate representing a peer review and fund allocation process to allow for entry in virtual research courtyards. A professional management structure has been established to ensure the continuous high quality of the translational awards that are allowed to enter the research courtyards. Every approved concept benefits from advice, guidance, and management, as well as financial support by the center.

Participating  
Research Institutes

Participating alongside the Universities of Leipzig and Halle-Wittenberg, Leipzig University Hospital and the Heart Center in Leipzig, are also the Fraunhofer Institute for Cell Therapy and Immunology, the Fraunhofer Institute for Mechanics of Materials, the Leibniz Institute for Surface Modification, and a number of biotech companies.

Educational  
Programme

Furthermore, the TRM develops and coordinates tailor-made educational programmes in order to integrate young scientists into interdisciplinary scientific fields. This is also of importance to support the translational process and to promote individual and professional development. The qualification offers meet all requirements for both international excellence and competitive-



ness in science, economy and management. All aspects of the translational process are considered, especially project management, intellectual property rights, and founding a business. The educational coordination is closely linked to staff development.

More information: [www.trm.uni-leipzig.de](http://www.trm.uni-leipzig.de)

### **Berlin-Brandenburg Center for Regenerative Therapies**

The BCRT, also established in 2006, is located in a newly reconstructed building at the Charité Campus Virchow Clinic, and is host to 26 newly implemented research groups. Scientists at BCRT are dedicated to using their findings from basic research and bioengineering to develop clinical applications and products. Financially, the BMBF, the States of Berlin and Brandenburg, the Charité and the Helmholtz Association are the prominent participants in the construction of the BCRT. In total, the available resources come to around 40 million euros in basic funding.

Highly interactive research is being conducted in four medical research fields that are crosslinked by indication-overlapping platforms on basic research, bioengineering, biomaterials as well as translational technologies. These areas are: immune-, cardiovascular-, and nervous and muscular systems, namely medical conditions such as fractures, heart disease or joint diseases. In order to arrive as quickly as possible at a therapy, the research efforts span individual disciplines and institutions. To these ends, researchers from a variety of different research institutes are in close cooperation.

In addition to the researchers at the Charité University Hospital, the Max Delbrück Center and the GKSS Research Center in Teltow, also participating are a large number of scientists from other institutions such as, the German Rheumatism Research Center, two Max Planck Institutes, the Free University and Humboldt University, as well as the University of Potsdam. Many companies are also involved, principally the pharmaceutical company Bayer Schering, as well as a number of biotechnology companies.

The “Berlin-Brandenburg School for Regenerative Medicines” is also based at the BCRT. Led by the Charité University Medicine Berlin, the school provides a three-year doctoral programme for up to 70 students. In this interdisciplinary concept, engineers, medical doctors, biologists and biochemists are given a fundamental understanding

Goal and Budget

Research Interests

Participating  
Research Institutes

Educational  
Programme

of the other disciplines required to develop new therapies in regenerative medicine. This is because interdisciplinarity and networking count among the most important pillars of this research field.

**Translation:  
Opportunity Check  
Infrastructure**

To efficiently advance novel therapeutic concepts from R&D into clinical practice, all BCRT projects are supported by the 'opportunity check' infrastructure. Traditionally, new academic ideas are reviewed for their market potential by the technology transfer offices of the universities after invention disclosures have been filed and significant R&D resources have been invested. BCRT scientists and clinicians check their concepts early on, during R&D phase and at the stage of idea development, by employing innovative risk management tools. To develop an optimized target product profile with an increased likelihood of entering the clinic and therefore of benefiting our patients, the 'Business Development' implements an infrastructure that allows for early definition of product development risks, market potential, patent analysis and patent strategy development, and the definition of regulatory approval strategies. Furthermore, the department "Clinical Development & Regulatory Affairs" supports all BCRT projects selected for development as a medicinal product or medical device for the large part defined by the Advanced Therapy Medicinal Product (ATMP), from first proof of concept through to regulatory approval and reimbursement.

**Stem Cell Registry**

The "European Human Embryonic Stem Cell Registry" (hESCreg) is also based at the BCRT. This database of some 650 hESC lines that have been derived in Europe and beyond (as of August 2009) is freely accessible. hESCreg is funded by the European Commission as a Specific Support Action under the 6<sup>th</sup> Research Framework Programme.

More information: [www.b-crt.de](http://www.b-crt.de)



## Reference- and Translation Center for Cardiac Stem Cell Therapy Rostock

The RTC in Rostock was founded in autumn 2008 by the German Ministry of Education and Research (BMBF), the Ministry of Economics of the federal state Mecklenburg-Western Pomerania, and industrial partners as an offspring of the Clinic and Policlinic for Cardiac Surgery of Rostock and the Research Center of Cardiac Tissue and Organ Regeneration. The BMBF is providing funding of 3.4 million euros over three years. In contact with the public authorities, additional relevant administrations, funding agencies and ministries, the RTC has a clear strategy for accelerating the translational process, i.e. the implementation of scientific and clinical results into innovative therapies. This includes the development of standardized methods for different translational process steps. In the future, the RTC will act as a reference center for further development and application of stem cell therapies of cardiac diseases.

### Goal and Budget

At the RTC, novel stem cell therapies for heart diseases are being investigated, and some are already being applied today. The aim of the RTC is to establish innovative examination methods enabling a healing of the damaged heart in the long-term. To achieve this aim, the RTC works in collaboration with basic, applied and clinical stem cell research groups in order to apply the scientific and clinical output in standardized therapies of high quality. The activities include: preparing applications for market approval of novel therapies, clarifying questions of reimbursement, extensive training of users, physicians and patients, and providing information for the public. In 2009, the RTC started a phase III clinical trial (see chapter Clinical Research).

### Research Interests

The RTC is working together with the Clinic and Policlinic for Cardiac Surgery of Rostock, the German Heart Institute Berlin, the Hannover Medical School, the Institute for Medical Informatics and Biometry, the Institute for Regenerative Medicine and Stem cell Therapy, and the Center for Developmental Biology in Kobe (Japan). Furthermore, collaborations with the BCRT, the CRTD, the TRM and REBIRTH and a number of biotech companies have also been established.

### Participating research institutes

In 2010, the RTC also offers an educational programme. It is participating in the Graduate school "Molecular Mechanisms of Regenerative Processes" established by the Medical Department of the University of Rostock.

### Graduate School

More information: [www.cardiac-stemcell-therapy.com](http://www.cardiac-stemcell-therapy.com)

### Regenerative Medicine in the Neckar-Alb Region

#### Goal and Budget

REGiNA was launched in May 2009, and is still under construction. A total of 30 partners in the region of Stuttgart and Neckar-Alb are working together with the University Hospital of Tübingen (UKT) to establish an application center for regenerative medicine that will carry innovative products and processes into health care on a trial basis. The BMBF is funding these measures up to 2013 with a total of 7.5 million euros. This sum is matched by private funding from business.

#### Research Interests

In the spotlight are four fields of research and development: the musculoskeletal system, the skin- and wound system, and the cardiovascular-, respiratory and urogenital systems. The construction of an application center stands at the heart of the initiative. Moreover, a target group-specific specialist consultancy that will be based on a yet-to-be-developed medical and patient information system (ÄPIS) is planned. The accompanying health economic analyses will be jointly carried out with sponsors. An accompanying evaluation of existing activities for the training of doctors and specialists is also included in the overall concept. The new treatment methods will be reviewed and evaluated from an ethical as well as socio-medical point of view.

#### Participating Research Institutes

Important pillars of REGiNA are the Center for Regenerative Biology and Medicine (ZRM) in Tübingen, and the Natural and Medical Sciences Institute (NMI) in Reutlingen. Also actively involved in the centers, among others, are the Fraunhofer Institute for Interfacial Engineering and Biotechnology (IGB) in Stuttgart, the Institute for Textile Technology and Process Engineering Denkendorf, the Universities in Bielefeld and Tübingen, as well as health insurance agencies and diverse companies active in the fields of biotechnology and medical engineering.

### Heidelberg Institute for Stem Cell Technology and Experimental Medicine

#### Goal, Budget and Research Interests

In 2008, the HI-STEM gGmbH was founded by the private Dietmar Hopp Foundation as the majority shareholder and the German Cancer Research Center (DKFZ) in Heidelberg. HI-STEM bundles the activities of the DKFZ, the Heidelberg University and the University Clinic in the areas of stem cell biology and stem cell therapy, in particular research into adult stem cells and cancer stem cells. HI-STEM is part of the BioRN Cluster "Cell-Based and Molecular Medicine in the Metropolitan Region Rhein-Neckar", which is funded by the BMBF

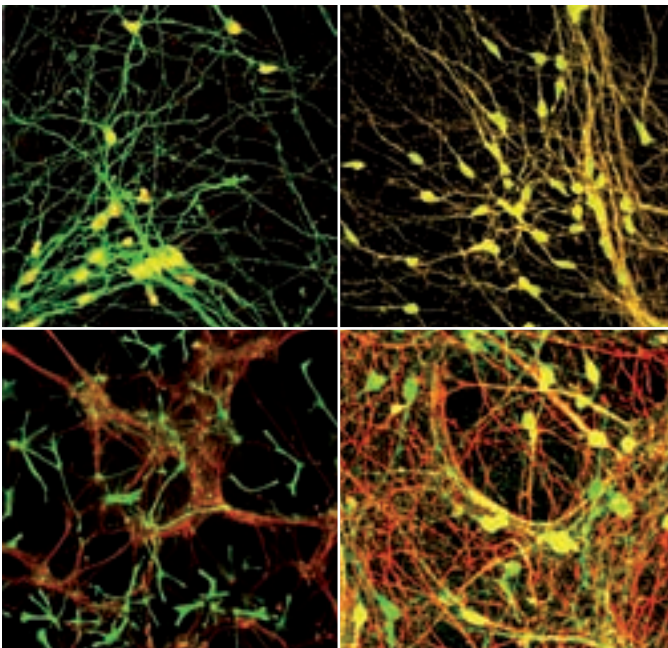


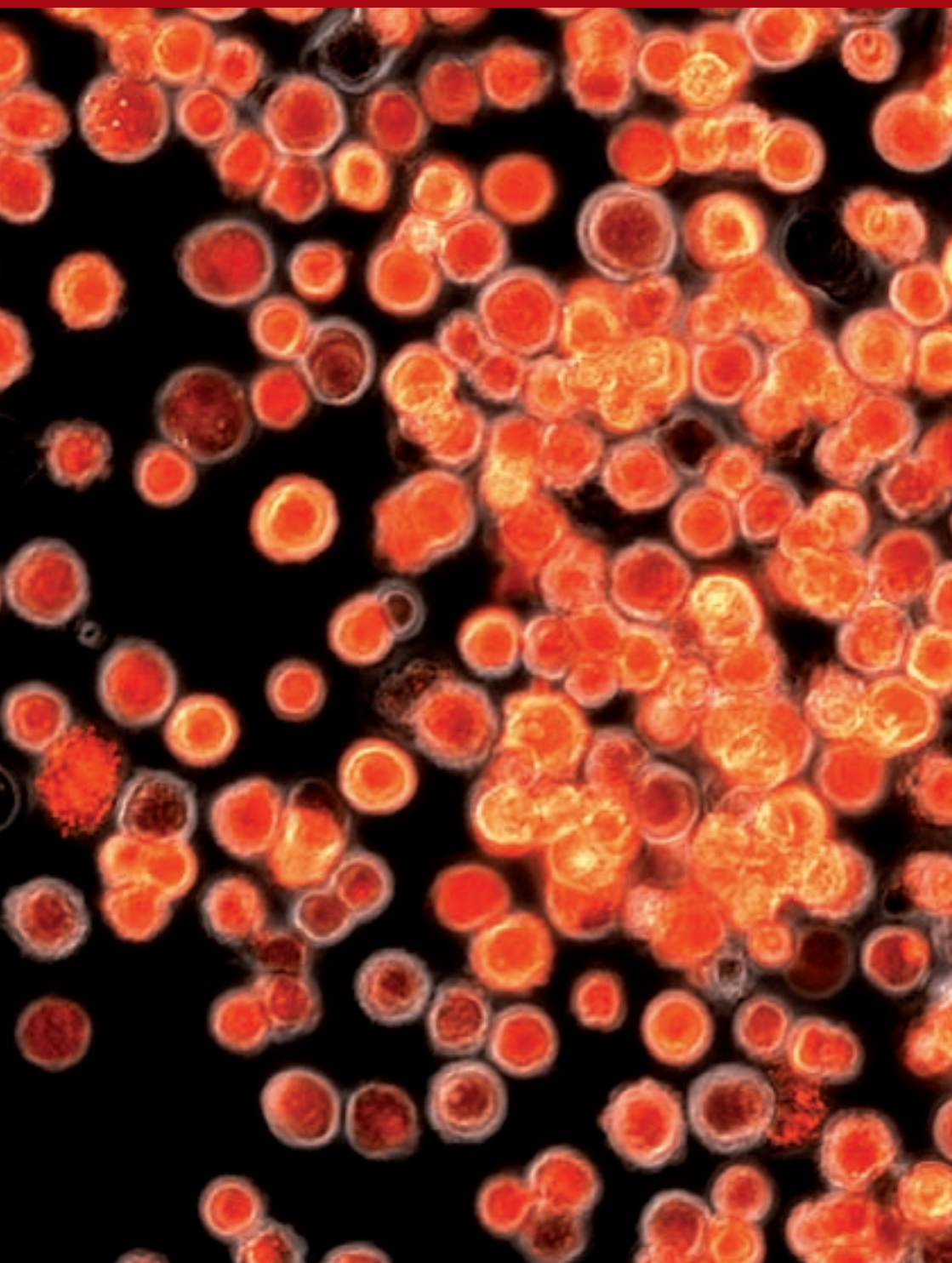
with 40 million euros for five years. Additional 40 million euros come from industrial partners of the BioRN Cluster. The Scientific Director of HI-STEM is stem cell researcher Andreas Trumpp, who responded to a call in 2008 from the DKFZ in Heidelberg, where he was serving as chair of the Department of Stem Cells and Cancer.

### Stem Cell Network North Rhine-Westphalia

In 2002, the federal state of North Rhine-Westphalia (NRW) initiated Germany's first stem cell network, which aims not only to bring stem cell scientists together but has also served as a bridge to the wider community. The stem cell network NRW is a state-wide organisation involving research facilities in Aachen, Bielefeld, Bochum, Bonn, Cologne, Düsseldorf, Essen, Münster and Witten/Herdecke. It covers virtually the whole spectrum of scientific issues in the field of adult and embryonic stem cell research. The Network consists of two working groups. One focuses on biomedical, the other on ethical, legal and sociological issues. In these groups top scientists, doctors, philosophers, theologians, sociologists and legal experts combine their expertise with a view to making stem cell research responsible and transparent

#### Goal





# Stem Cell Research

Research on stem cells in Germany focuses on the areas of embryonic stem cells, adult (tissue-specific) stem cells, cancer stem cells, research on new artificial sources of pluripotent stem cells using, among others, the iPS technique, as well as natural alternatives such as testicular stem cells.

The legal framework for research involving human embryonic stem cells is more restrictive regulated in Germany than in other European countries. The production of hESC lines is prohibited by the German Embryo Protection Act (Embryonenschutzgesetz). Since 2002, the Stem Cell Act (Stammzellgesetz, amended in 2008) has regulated work with hESC lines in Germany with the cut-off date regulation: Accordingly, researchers are only permitted to import hESC lines from abroad that were derived before 1 May 2007. Strict conditions apply: Each individual project must meet high academic standards ("eminent research aims" and no available alternatives), it must be reviewed and approved by the Central Ethics Commission on Stem Cell Research at the Berlin-based Robert Koch Institute, which regulates stem cell research in Germany. Besides working with hESCs, more and more researchers are interested into alternative stem cells. This research has been the subject of specific support from government funding programmes. This goes some way to explaining the growing scientific expertise in Germany particularly in the area of adult stem cells.

## Embryonic Stem Cells

Up to March 2010, more than 50 projects at German research institutes were granted approval by the Robert Koch Institute, thereby authorizing the participating scientists to import hES cells from abroad. The number of successful applications has increased steadily since the first import authorization was granted in 2002; in 2009, 14 groups were granted authorization. In the project descriptions, a change in application requirements can be seen, however. In past years, the hESCs were for the most part used as a potential source for cell replacement therapy, and for tissue engineering. A wide range of more recent research projects are aimed primarily at the use of hESCs as a

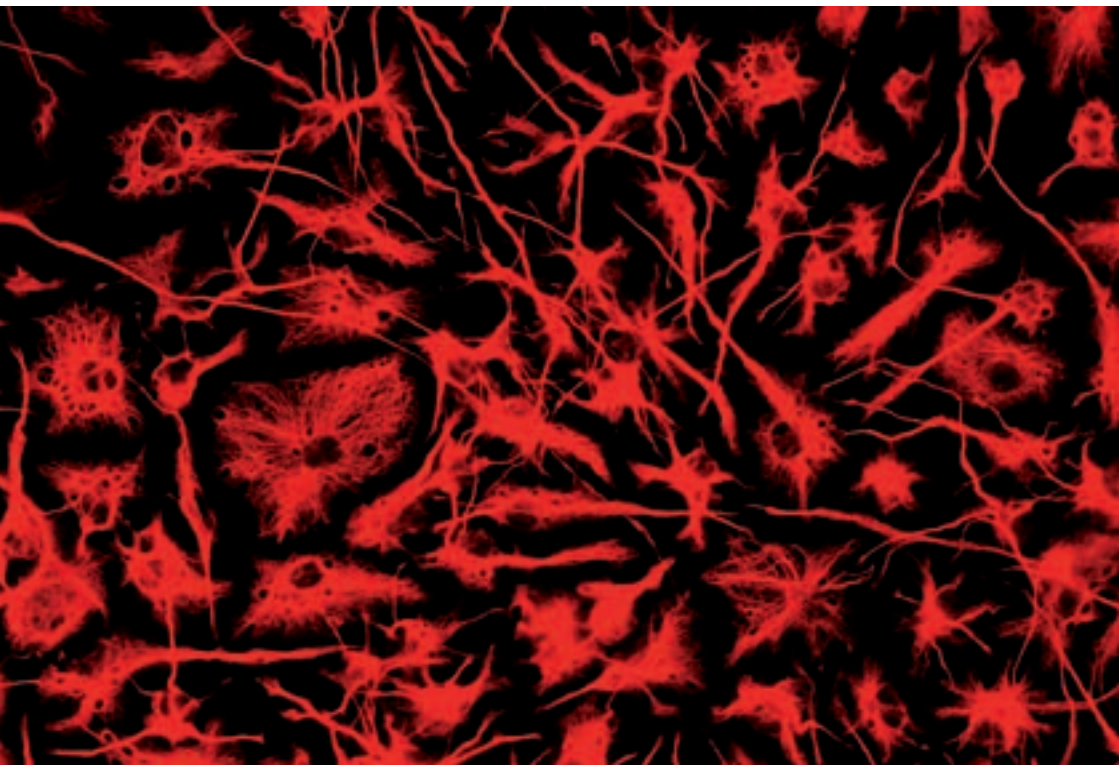
comparison standard for the characterization of induced pluripotent stem cells or pluripotent cells from the germ line.

Cardiomyocytes  
derived from  
ES Cells

Pioneering work based on ESCs in Germany is taking place at the laboratories of Jürgen Hescheler at the Institute for Neurophysiology in Cologne and Oliver Brüstle of the Institute for Reconstructive Neurobiology at the University of Bonn. Hescheler's team has succeeded in improving heart function in infarct-damaged mice using cardiomyocytes derived from ES cells. With approaches that are based on hES cells, the Cologne-based researchers are focused in particular on differentiating heart muscle cells, and on optimizing these for use in pharmacological and toxicological testing.

Neural Stem Cells  
derived from  
hES Cells

Brüstle's team has developed a process that enables a specific form of neural stem cell to be derived from hESCs. These neural stem cells can be used for long periods to differentiate them into a variety of neurons and glia. This method saves time, can be standardized and automated, and enables researchers to obtain highly purified neurons that are also suitable for drug discovery and pharmacological tests.



## Tissue-specific Stem Cells

Research on tissue-specific (adult) stem cells in Germany is traditionally a major area, and has for some years been the subject of targeted funding from the BMBF. Alongside research into different sources of adult stem cells in the body, there is a clear focus on the study of the biology and therapeutic potential of mesenchymal stem cells (MSCs) from the bone marrow. Research on hematopoietic stem cells from umbilical cord blood (CB-HSCs) is also an emphasis of current projects. Extensive translational research is taking place in the field of cardiovascular cell therapy with bone marrow stromal cells (see chapter Clinical Research).

Mesenchymal stem cells (MSC) are multipotent skeletal precursor cells that can develop into a number of different cell types, such as bone, cartilage, fat and tendon. For this reason, they are being considered not only as a source of cells for tissue regeneration. The high clinical potential of MSCs derives from the fact that the cells release growth and differentiation factors into their surroundings, and simultaneously possess immunomodulatory properties. Nevertheless, translating preclinical results to clinical practice is no easy matter: MSCs must first be better understood, and standardized protocols for purification and application must also be developed. A number of German research consortia are specifically occupied with characterizing MSCs. A researcher team headed by Anthony Ho of the University of Heidelberg and Albrecht Müller of the University of Würzburg is studying the genetic and epigenetic profile of MSCs, and is exploring the suitability of the cells as a starting material for iPS cell reprogramming. Dresden-based materials scientists at the CRTD are studying the stem cell niche and the growth conditions for the cells on biomaterials. A consortium led by Jochen Seissler of the Ludwig Maximilians University Munich is investigating the supportive application of MSCs as an immunosuppressive therapy following pancreatic islet transplantation.

Mesenchymal  
Stem Cells (MSCs)

German researchers are also addressing the area of stem cells derived from umbilical cord blood. Among others, an interdisciplinary consortium of researchers from Aachen, Würzburg and Hannover is occupied with the development of a culture method that enables blood-forming stem cells as a limited resource to be expanded in the laboratory. Thereby, a variety of growth factors, substrates, and the epigenetic characteristics of the CB-HSCs are being tested to determine the best recipe for effective expansion. Following tests on animals, the developed cord blood cells are likely to be used to patients

Umbilical Cord  
Blood Stem Cells  
(CB-HSCs)



suffering from acute myeloma leukemia. In turn, research groups such as the group headed by Ulrich Martin of the Medical University of Hannover and the REBIRTH Center for Regenerative Medicine are investigating the potential of cord blood stem cells as a suitable cell resource for iPS cell reprogramming.

### **Germline-derived Stem Cells (GSCs)**

In recent years, a number of German groups have concentrated on the study of “natural” alternatives to hESC and induced pluripotent stem cells, and have been conducting important pioneering work in the field. Thereby, testicular stem cells have been shown to carry extremely diverse developmental potential. A number of German research consortia are now investigating testicular stem cells as a possible direct natural source of pluripotent stem cells. In 2006, Gerd Hasenfuß and Wolfgang Engel from the University of Göttingen drew colleagues’ attention to testicular tissue. They have since extracted pluripotent germline stem cell lines (spermatogonial stem cells, SSC) from the gonads of adult mice. In autumn 2008, a working group led by Thomas Skutella of the University Hospital in Tübingen likewise succeeded with this approach, only this time with humans: The researchers extracted and cultured cells with pluripotent characteristics (human germline-derived stem cells, haGSCs) from the testicular tissue of an adult.

Hans Schöler and his working group at the Max Planck Institute for Molecular Biomedicine in Münster recently succeeded in a mouse model in transforming the adult germline cells into pluripotent cells using specific culture conditions. A consortium of researchers from Münster, Neustadt, and Bonn is now investigating whether cardiac muscle cells can be derived in a controlled manner using GSCs from mice, pigs or humans. These will be studied in detail for their suitability for cell replacement therapies and drug testing.

### **Neural Stem Cells**

A number of German research institutes are occupied with the regenerative capacity and plasticity of the adult brain, a capability that was only identified some years ago. The adult brain contains stem cells in the hippocampus and the olfactory bulb, exactly those regions that malfunction during neurodegenerative diseases such as Parkinson’s. Researchers led by Gerd Kempermann at the Research Center for Regenerative Therapies Dresden (CRTD) are characterizing these neural stem cells in detail: How and when are new nerve cells created in the hippocampus? What role does cognitive and physical activity play in adult neurogenesis? How do these cells survive? The Dresden-based researchers are also working on establishing neural stem cell lines that can be cultured in the laboratory and that are intended for use

in basic research. Some years ago, Magdalena Götz from the Helmholtz Center in Munich likewise demonstrated that glial cells take on the function of neuronal stem cells at injury sites in the brain. These are then capable of producing new nerve cells. Götz is examining how specific regulatory proteins control adult neurogenesis, and how these could be possibly selectively stimulated throughout the brain. The conceivable significance of a cell replacement therapy is the focus of another, broad-based research consortium that includes the participation of scientists from Munich, Dresden, Jena, Regensburg and Erlangen-Nuremberg. The consortium deals with how nerve cells cultured from stem cells are integrated into the brain and its neural network, either through the transplantation of nerve cells or through stimulation aided by specific factors.

Even adult stem cells age and slow down in their role of a continuously regenerating source of cells. Research groups in Germany are investigating this phenomenon of stem cell aging. Hartmut Geiger from the University of Ulm is studying the immediate vicinity of blood-forming (hematopoietic) stem cells in the bone marrow. To date, analyses suggest that in aging stem cells, the interaction with the surrounding stem cell niche no longer functions properly, and the cells become hyperactive and mobile. Geiger is studying which signaling mechanisms are responsible for this aging.

### Stem Cell Aging

The functioning of adult stem cells in muscle tissue (satellite cells) remains poorly understood. A collaborative project has the aim of better understanding the regenerative capacity of muscle stem cells, and using this knowledge for the future treatment of genetic diseases such as muscular dystrophy. A research team led by Thomas Braun from the Max Planck Institute for Heart and Lung Research in Bad Nauheim is using a mouse model to investigate the molecular mechanisms and signaling pathways that play a role in the maintenance of stem cells in muscle tissue. A team led by Markus Schülke-Gerstenfeld from Charité University Medicine Berlin is hoping to improve muscle stem cells' behavior in cell cultures, which to date has been a problematic issue.

### Muscle Stem Cells

## Induced Pluripotent Stem Cells

The potential and rapid progress of cell reprogramming has significantly changed the German stem cell research environment. The production of induced pluripotent stem cells (iPSC) with the expression of pluripotency-associated transcription factors is compatible with the German legal framework (Embryo Protection Act and Stem Cell Act).

Since 2008, numerous projects and consortia working on or with the production of iPS cells have been funded by the BMBF. The central goal of these measures is the further development of iPS technology. For example, in Hans Schöler's laboratory in Münster, the number of factors required to reprogram mouse neural stem cells was reduced from four to just one, namely the transcription factor Oct4. At this time, experiments are taking place involving small molecules that are also set to aid the reprogramming process.

#### Disease-specific iPS

A variety of project groups are concentrating on the production of disease-specific iPS cells for the study of the molecular causes of diseases. Cells from patients with nervous disorders (Bonn), specific heart conditions (Cologne) or metabolic liver diseases (Hannover) are being used in the reprogramming process. James Adaye from the Max Planck Institute for Molecular Genetics in Berlin is characterizing iPS cells from Morbus Alzheimer patients.

#### Alternative Cell Sources for iPS Reprogramming

In turn, a team headed by Jürgen Hescheler from the University of Cologne is carrying out a large-scale project to examine whether iPS-derived heart muscle cells are suitable for transplantation into infarction-damaged mouse hearts, or for pharmacological testing. The most widely used laboratory protocols rely to a great extent on skin cells as the basis for reprogramming. Adult stem cells represent an alternative source of cells. Recently, a team led by Ulrich Martin of the Hannover Medical School (REBIRTH) announced the successful production using cord blood stem cells. These are particularly well suited for the production of iPS, as they have accumulated few muta-



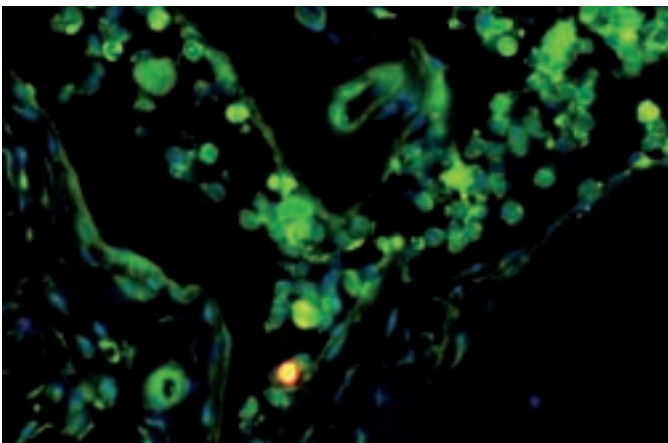


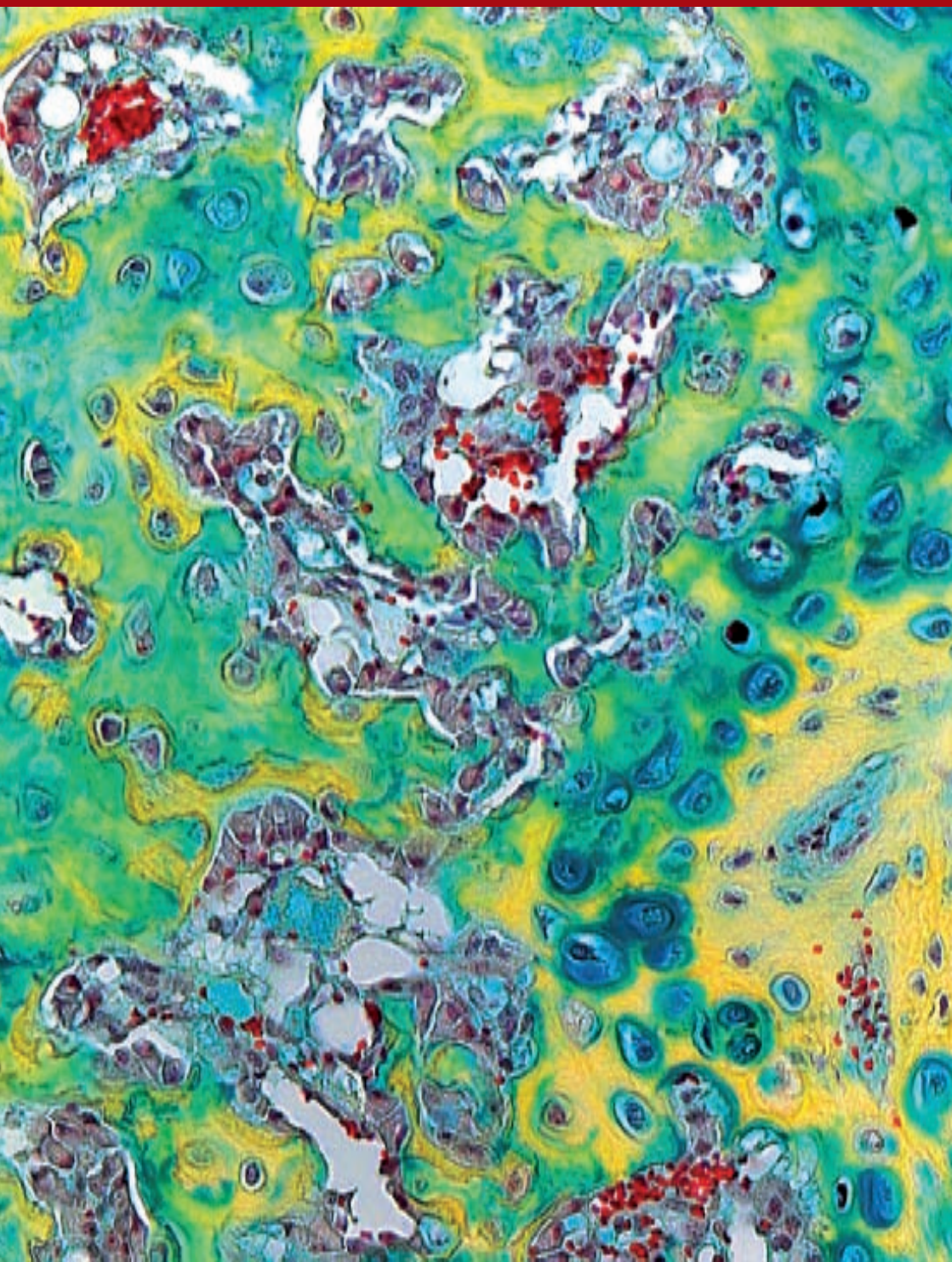
tions in their genetic information. Other research groups are examining mesenchymal stem cells for their suitability as a starting material for the reprogramming (MSC-iPS).

### Cancer Stem Cells

There is growing opinion that cancer is a stem cell disease. Stem cells have now been discovered for a whole range of cancers, such as leukemia, breast-, colon- and prostate cancer, and even for brain tumors. The stem cell theory also explains why cancer therapies so often fail, because tumor cells deploy tactics that can make them resistant to radiation and chemotherapy. Researchers at the HI-STEM in Heidelberg and the German Cancer Research Center (DKFZ) have demonstrated in mice that hematopoietic stem cells from bone marrow evade the effects of chemotherapy through a state of dormancy. The studies verify that the messenger substance interferon-alpha activates the dormant tumor cells in the bone marrow (metastasis-inducing cancer stem cells, MICs), thereby making them vulnerable for subsequent chemotherapy. The research group led by Trumpp has now developed a custom-designed xenograft model in mice for the identification of MICs from human blood or bone marrow. The model enables the targeted search for active ingredients directed specifically against target molecules on the MICs. A clinical study examining the new treatment approach with leukemia patients in Heidelberg, Jena and Mannheim is currently underway at the HI-STEM (see chapter Research infrastructure).

Activation of  
Metastasis-inducing  
Cancer Stem Cells





# Regeneration Technologies Research

German research and development in the area of tissue engineering and biomaterials research occupy a dominant position in international comparison. Germany is able to draw on many research traditions in the fields of medical technology, materials science and engineering, which, in combination with a highly developed medical and clinically-oriented research infrastructure, provides an important basis for the required interdisciplinary cooperation. In addition to the numerous academic and research institutions specialized in this field of research, there are more than 60 biotechnology companies operating in the field of regenerative medicine that drive the area forward. Bundled in each of the major translational research centers for regenerative medicine in Dresden, Hannover, Berlin, Leipzig and Tübingen are competencies for regeneration technologies (see chapter Research Infrastructure).

Furthermore, the Fraunhofer Association, Germany's largest organization for applied research, has five institutions in a life sciences network that is working on aspects of regeneration technologies for practical application. Included in the network are the Fraunhofer Institute for Cell Therapy and Immunology (IZI) in Leipzig, the Fraunhofer Institute for Interfacial Engineering and Biotechnology (IGB) in Stuttgart, the Fraunhofer Institute of Toxicology and Experimental Medicine (ITEM) in Hannover and the Fraunhofer Institute for Biomedical Engineering (IBMT) with sites in St. Ingbert and Lübeck.

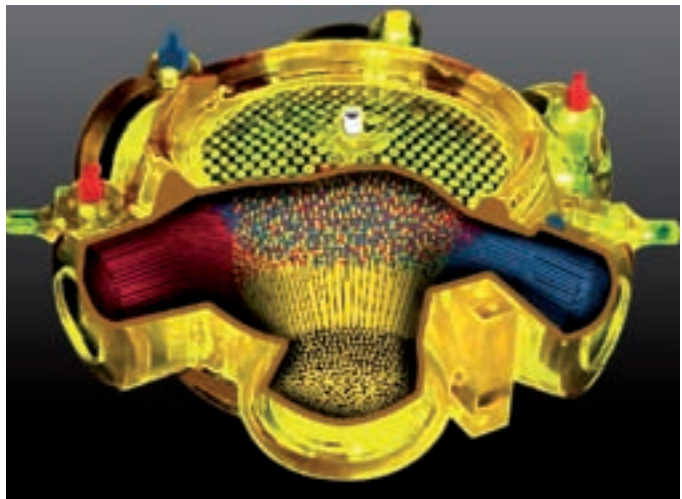
## Tissue Engineering

A number of German research groups are engaged in the further development of culture techniques for the cultivation of tissues and bioartificial organ systems. A central objective of ongoing projects is the improvement of methods towards a standardized cell culture and a controlled seeding of scaffolds according to the rules of Good Manufacturing Practice (GMP), as required for future medical applications.

German biotechnology firms have already brought a range of tissue engineering products to the market for skin replacement to treat

burns and chronic wounds, and for cartilage grafts following injury. The challenges for tissue engineers, however, remain in the area of complex organ systems, for example the production of a bioartificial liver or an artificial kidney, which would find future application for optimized dialysis treatment, or for drug development testing. The researchers are working meticulously with procedures whereby multiple cell types are grown together in a culture (co-cultures) for the production of complex bioartificial organs. This is ultimately aimed at the creation of three-dimensional organ models that mimic the natural situation in the body as realistically as possible. A complicated issue in the creation of more complex organic systems is the adequate supply of oxygen and nutrients via an artificial blood vessel system (vascularization). The construction of modular bioreactors that enable cells to be cultured over periods of weeks is also being worked on. Researchers are experimenting with various cell sources as raw materials for bioartificial constructs, which, alongside stem cells, will above all involve primary cells taken from patients. Questions of preservation over shorter or longer periods (cryopreservation) are also being examined. In addition, German research institutes, for example the Fraunhofer IBMT in St. Ingbert, Saarland, with one of the most modern, fully automated biobanks in the world (for stem cells, among others), are leaders in the field of cryobiotechnology.

The following few examples illustrate the diversity of the conducted research:





The development of bioartificial organs is already comparably advanced for the kidney and the liver. The team headed by Heike Walles of the Fraunhofer Institute for Interfacial Engineering and Biotechnology (IGB) in Stuttgart recently succeeded in this area in the development of an bioartificial liver model that is interlaced with a functional vascular system. In the model, liver cells are cultured together with endothelial cells. A decellularized matrix from small pig intestine – still containing a rudimentary framework of blood vessels – is seeded with the two cell types. The dynamic 3D liver model can be cultured for periods of weeks at a time in a special bioreactor. It is particularly well suited as a drug-testing system, and could provide an alternative to animal experimentation. Augustinus Bader's team at the University of Leipzig (TRM) is experimenting with similar liver systems.

#### Liver and Kidney

Other groups such as those headed by Katrin Zeilinger and Jörg Gerlach of the Charité University Medicine Berlin (BCRT) are developing liver bioreactors on the basis of synthetic hollow-fibre capillaries, which are intended to be used outside the body for treatment support following acute liver failure. Initial pilot studies in patients with these biohybrid organs have been successful, and larger clinical trials will be necessary. In turn, the team led by Will Minuth from the University of Regensburg has constructed a bioreactor system in which rabbit stem cells develop into three-dimensional tubules – the smallest functional units of a kidney – in an artificial environment of polyester fleece fabric.

Although the cultivation of bioartificial myocardial tissue is still in an early experimental stage, promising progress has been made in the creation of adaptable heart valves using tissue engineering. For example, Axel Haverich and colleagues at the Medical University of Hannover (REBIRTH) are using donor heart valves that are decellularized until all that remains is a fine collagen scaffold, which can be repopulated with cells. These are extracted from the patient's own blood, and cultivated on the donor heart valve scaffold. These heart valves have already been deployed with a number of young patients – children above all can benefit from these valves that grow with the patient. Stefan Jockenhövel from the RWTH Aachen University has also developed similarly adaptable heart valves. The difference here is that in the Aachen-based procedure, the valves are constructed using ingredients taken entirely from the patient's own body. The cells required for this originate from the blood vessels or the umbilical cord of the patient. In addition, a so-called fibrin gel matrix is prepared, a kind of supporting corset made from a blood protein. In a special procedure, the matrix is cast together with the cultured cells into the

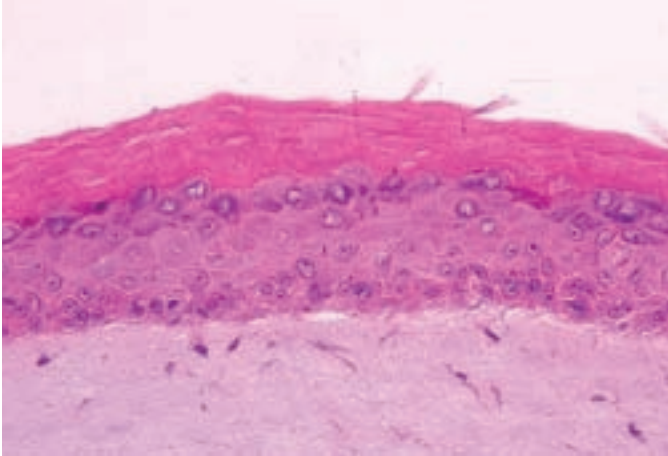
#### Cardiovascular Tissue Engineering



shape of a heart valve, before being further bred and trained in a bioreactor. The heart valves then undergo testing in animal models such as sheep for their resilience and reliability. The reconstruction of the complexly structured heart muscle replacement tissue is a more difficult issue. Here, the lack of suitable cell sources remains a significant bottleneck. A network of researchers from Göttingen, Hannover and Munich are hoping to tackle this problem: through genetic modification, cardiac muscle cells will be derived in vitro from embryonic pluripotent stem cells (GSCs and iPSCs). It is planned to develop these in three-dimensional cultures into living cell clusters.

### Skin Engineering

The method of “skin from hair roots” was developed for the market by the Leipzig-based biotechnology company Euroderm together with the Fraunhofer Institute for Immunology and Cell Research (IZI) in Leipzig. Thereby, skin stem cells from the root sheath of the hair is propagated in a cell culture for two to three weeks; the resulting two-layered epidermis grafts are used for wound healing. A different procedure has been developed by a consortium of scientists from Berlin, Kiel and Munich. The Berlin-based biotech company Probiogen, specialists in cell cultivation, contributed to this project with a specially developed bioreactor. Here, the researchers hope to go one step further with their skin model, and are working towards a model that is furnished with hair. This will be of interest in particular for cosmetics manufacturers for testing purposes. For this “skin with hair,” the Berlin-based researchers begin with hairs plucked from the head. They then extract different types of adult stem cells from the root region of the hair follicles. Using these cells, it is then possible



to cultivate a two-layered epidermis. The researchers are now also hoping to use their technique to produce artificial hair follicles. So far, the resulting follicles are smaller and thinner than their natural counterparts. In the long term, it is planned to connect the cultured follicles to blood vessels to keep them alive for days and weeks at a time. Researchers and engineers at the Fraunhofer Institute for Manufacturing Engineering and Automation (IPA) in Stuttgart have developed the first system worldwide which fully automates the production process of human skin equivalents. A prototype will be running by the end of 2010 and produce functional 5,000 skin equivalents per month at a cost below \$44.

Bone and Cartilage are central fields in tissue engineering. A number of German biotech companies, among others TETEC, BioTissue Technologies and Codon, have already brought autologous cell products to the market in this area. These include products for use in the treatment of local cartilage defects, for example by means of autologous chondrocyte transplantation (ACT). Thereby, the patient's own cartilage tissue is cultivated on a matrix and implanted into the defective site. At this time, only small joint defects and young patients can be treated with this method. In the framework of the REGiNA network (see Chapter Research Infrastructure), researchers from Tübingen and Reutlingen are developing new technologies that are intended to enable particularly resilient articular cartilage to be cultivated in dynamic bioreactors. Prasad Shastri's team at the Centre for Biological Signalling Studies (BIOSS) in Freiburg has developed a method to generate large pieces of hyaline cartilage, which are grown within

### Bone and Cartilage

the patient's body. This *in vivo* tissue engineering is based on an biocompatible gel that is injected in the subperiosteal space of the shinbone, thereby using this region as a bioreactor. The resulting lack of oxygen seems to induce and stimulate the development of hyaline cartilage, at least in a rabbit model. The new tissue can be used for transplantation into osteochondral defects and adapts well to its new environment. Within the next years, Shastri's team plans to test the *in vivo* engineering approach within human patients.

### Peripheral Nervous System

Autologous disc cell transplantation (ADCT) is also being further developed by German biotech companies, and their application is currently being tested in clinical trials. Regenerative therapies for bone defects are aimed in particular at the production of implants made of synthetic biomaterials that will boost regeneration in the body. A number of research groups are dealing with the processes that take place during bone healing. The team led by Georg Duda from the Berlin-Brandenburg Center for Regenerative Therapies (BCRT) has investigated the different factors and cells that are significantly involved in the early stages of bone healing. In addition to the application of growth factors, the researchers also have a therapy in their sights that assists bone healing, which involves mesenchymal stem cells (MSCs) from bone marrow. It has been demonstrated in animal tests that bones heal more quickly at the break point when pre-differentiated osteogenic cells are injected into the bone fissure. Especially for older patients, it is hoped that this could aid healing process in the treatment of bone defects.

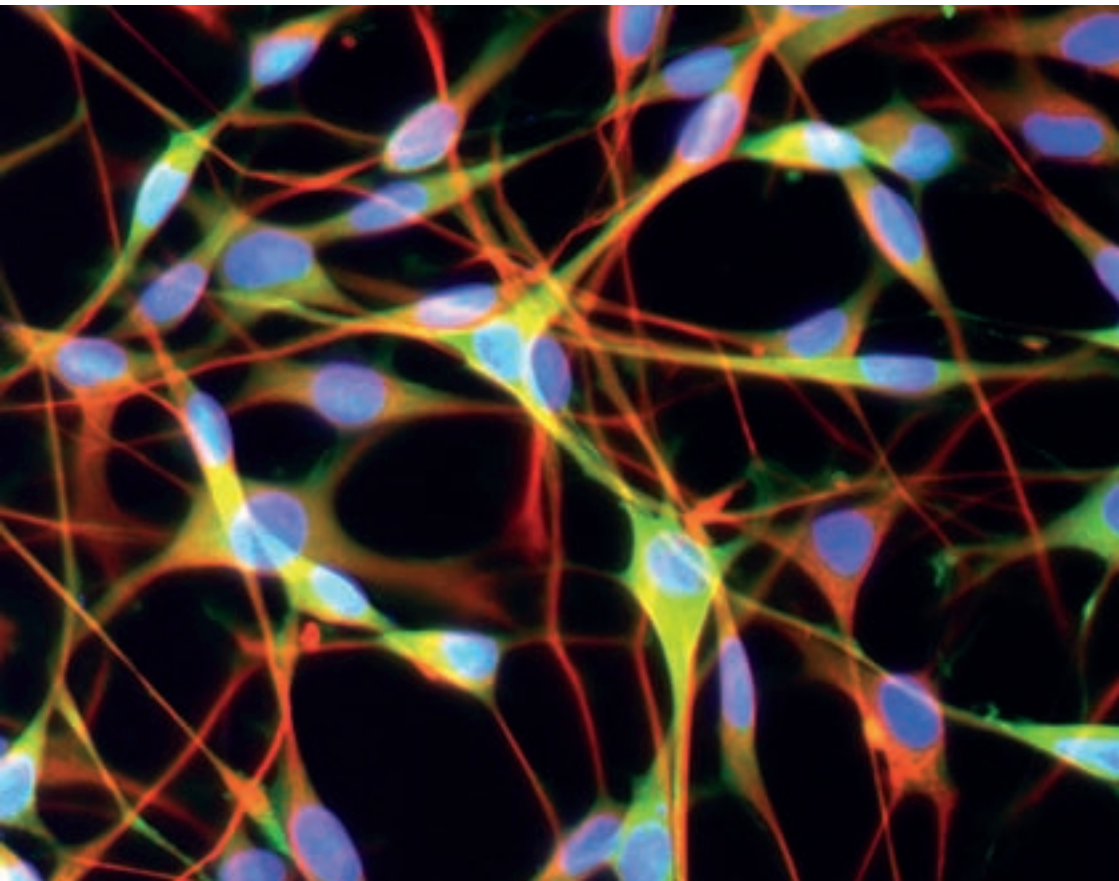
Paralysis and other disabilities often occur when nerves are severed during a serious injury. Axons can regenerate in the body, although they often lack orientation over long distances, and can sprout somewhat chaotically. To bridge this, the patient's nerve fibers are transplanted into the site.

Several groups in Germany are working on bioartificial nerve guidance channels, which represent an alternative approach. A group of physicians headed by Ahmet Bozkurt of the university clinic at RWTH Aachen is developing nerve guidance channels together with the biotechnology company Matricel in Herzogenrath. In a patented process, extremely fine hollows are milled into a collagen gel using fine ice crystals. The resulting internal tubes are then populated with the patient's own Schwann cells – the natural supportive cells in nerves. These cells accumulate longitudinally, and attract the growing nerve fibers by secreting growth factors. Previous studies have shown that the populating Schwann cells appear



to be key for successful artificial nerve guidance channels. The researchers are currently testing their biohybrids in animal studies, whereby the constructs are implanted in rats with severed leg nerves. After a number of weeks it can be seen that nerve fibers sprout effectively into the guiding structure, and that the regenerating fibers are indeed able to reach the muscle, where they stimulate contraction.

Scientists from the Natural and Medical Sciences Institute (NMI) in Reutlingen, which is also involved in the REGiNA network, are working on a similar approach. Their nerve guidance channels consist of extremely fine hollow collagen tubes, which degrade after a period of time, and they are filled with a mesh of fine polymer filaments. These structures are seeded with the patient's own Schwann cells, and are loaded with growth factors. A future research goal: With specially designed coatings, the researchers hope to encourage the Schwann cells to populate the structures without external assistance.



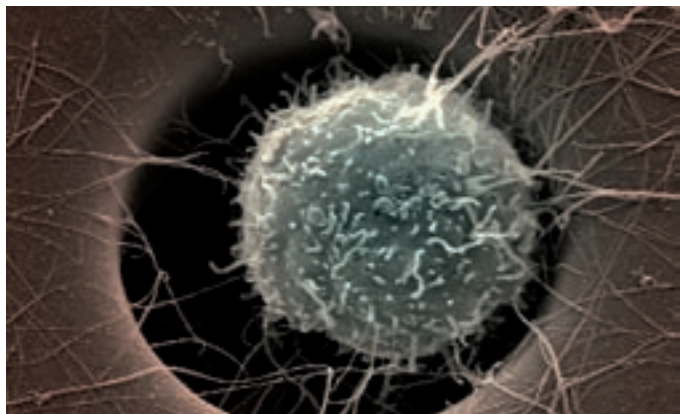
## Biomaterials

Research into biomaterials has made considerable progress as a result of increased molecularization and applied nanotechnology. Materials in implants can be equipped with continuously advancing biomimetic properties that improve both cell seeding and integration in the body. It is hoped that these materials will also stimulate regeneration in the body, and ideally be biodegradable over time. Polymeric biomaterials are commonly loaded up with drug molecules or growth factors, which can then be released in a controlled manner. Regenerative processes take place limitedly and locally, and must be carefully controlled. Specific drug delivery systems that can targetedly release the biomolecules must be developed for eventual application. Projects to develop appropriate and tailor-made biocompatible materials for medical applications are underway in most of the major centers for Regenerative Medicine in Germany (see chapter Research Infrastructure).

The following examples of ongoing projects demonstrate the diversity of approaches being pursued:

### Shape-memory Polymers

A team headed by Andreas Lendlein at the GKSS in Teltow near Berlin (BCRT) is researching biodegradable polymers that can be tailored for medical applications. Other types of advanced polymers are stimuli-sensitive, and can change shape according to temperature stimuli. Upon a heat stimulus of 60°, these intelligent shape-memory polymers transform permanently from a stretched rod into a spiral form. The stimuli-sensitive polymers are currently being tested for use in surgery or in drug delivery systems.

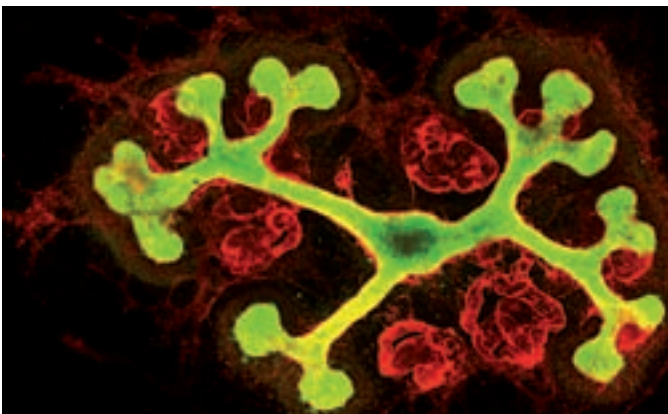


Likewise, biomaterials researcher Carsten Werner at the CRTD in Dresden, is using bioartificial polymer materials in attempts to replicate the stem cell niche of hematopoietic stem cells (HSCs). To do this, the team has constructed silicon frameworks containing microcavities. The surface of the cavities is coated with specific polymers and growth factors, which has the aim of realistically mimicking the natural microenvironment of a stem cell in the body. The cavities are so small that only a single stem cell can fit in each one, directly affecting the niche walls. Thereby, the researchers will be able to do more than just carefully study and influence the development of the artificial stem cell niche: Werner also hopes to multiply donor stem cells in the laboratory using the new culture method.

Reconstructed  
Stem Cell Niches

A consortium of researchers from Dresden, Freiberg and Lübeck is working on some unusual biomaterials, namely absorbable scaffold materials made using marine collagens. The polymers that will eventually be seeded with cells derive from jellyfish or fish skins. The end result is hoped to be cylinders of bone and cartilage. Marine collagen is regarded as particularly compatible for these purposes. The cartilage component will be made from a type II collagen that is isolated from jellyfish. The natural structure of this collagen matrix provides the chondrocytes with a suitable environment for forming healthy new tissue. The bone component will be made from a type I collagen of fish skin and nanoscopic hydroxyapatite crystals. This combination closely mimics the extracellular matrix of bone, and stimulates stem cells to form bone tissue. The resulting replacement tissue is intended in particular for defects in articular cartilage.

Biomaterials using  
Marine Collagens





# Clinical Research

With its many clinics and closely cooperating research groups, Germany can enjoy a strong reputation in regenerative medicine as a location for clinical studies. Concerning cell therapies, German scientists have a traditional emphasis on autologous approaches. A special focus of applied research in regenerative medicine is the treatment of patients with acute heart infarction with a therapy that employs autologous stem cells taken from bone marrow. Large clinical studies, which could prove groundbreaking for the approval of stem cell therapy, are already underway in this area in a number of medical centers in Germany.

Gustav Steinhoff at the RTC in Rostock is developing a process that utilizes bone marrow stem cells from the patient for treatment following heart infarction. Thereby, CD133+ cells are isolated from the bone marrow of the heart patient shortly before heart surgery. During ongoing bypass surgery, these cells are targetedly injected into the heart muscle, and specifically in the area surrounding the infarct-damaged tissue (intramyocardial method). About 140 patients have treated with this method to date. It could already be demonstrated that the pumping capacity of the heart is increased by around ten percent compared to untreated patients, and without noticeable side effects. In October 2009, the physicians launched a large-scale phase III study (called PERFECT), which will treat up to 142 patients. This study will be double-blind and placebo-controlled, and will ultimately decide whether the therapy will gain approval. The German Heart Center in Berlin and the Medical School in Hannover are also participating. The study is supported by the state Mecklenburg-Western Pomerania and the BMBF, and is expected to be completed until 2012.

Heart Stem Cell  
Therapy  
in Phase III

Further stem cell therapies for infarction of the heart are in the clinical phases in other locations. An intracoronary approach has been developed by researchers headed by Düsseldorf-based former cardiologist Bodo-Eberhard Strauer, one of the pioneers of cardiac stem cell therapy and now in the advisory board of the RTC. Thereby, extracted bone marrow stem cells are directed into the infarcted area via the coronary arteries. Positive effects have also been achieved with this method.

Already some years ago, the REPAIR AMI study (Phase III), one of the largest adult stem cell studies so far, also demonstrated positive effects with cardiac patients. The study conducted at the Johann Wolfgang Goethe University in Frankfurt was headed by Stefanie Dimmeler and Andreas Zeiher. A further study on a possible cell therapy for heart infarction comprising autologous skeletal muscle cells is being conducted by the US biotech company Bioheart Inc. Here, a number of German hospitals are participating in a clinical phase II trial (SEIS-MIC) – an example of how the German clinical research environment is an attractive location for cell therapy studies.

### Allogeneic Cell Therapy

Although autologous therapies play a major role in the German research landscape, in the meantime allogeneic cell therapy approaches have also become a subject of examination at German study centers. For example, in 2009 a phase I trial was launched at the Berlin-Brandenburg Center for Regenerative Therapies (BCRT), in which patients with peripheral vascular occlusion diseases are treated with mesenchymal stem cells from the placenta (PLX-PAD study). Participating in this study is an Israeli biotech company and clinics in the USA (Duke University Medical Center/North Carolina; Cardiology PC/ Birmingham, Alabama).

Other cell therapy approaches, including for the treatment of stroke, and of neurodegenerative diseases such as Parkinson's, are also being investigated by a number of German research groups. In most cases, these studies are still in the experimental or early clinical phases. A group of neurosurgeons headed by Thomas Brinker from the International Neuroscience Institute in Hanover, for example, is conducting a pilot study into an allogeneic stem cell therapy following the "tea bag approach": A small container of genetically modified stem cells from bone marrow is inserted in the brain of stroke patients. Like a tiny pharmaceutical factory, the stem cells release growth-promoting and anti-inflammatory proteins. The exogenous stem cells are encapsulated with an alginate membrane, thus preventing rejection by the immune system. After two weeks, the stem cell bags are removed in a follow-on operation. This approach has already been proven to have a healing effect in animals.

### Immunomodulatory Therapies

Cell therapy aiming to repair and support derailed immune systems is increasingly used as a new approach in regenerative medicine in order to combat cancer or infections. A number of successful studies have already paved the way for immunomodulatory therapy. A special platform of the Berlin-based BCRT is focusing on translating immune cell therapy into the clinic. For example, researchers have

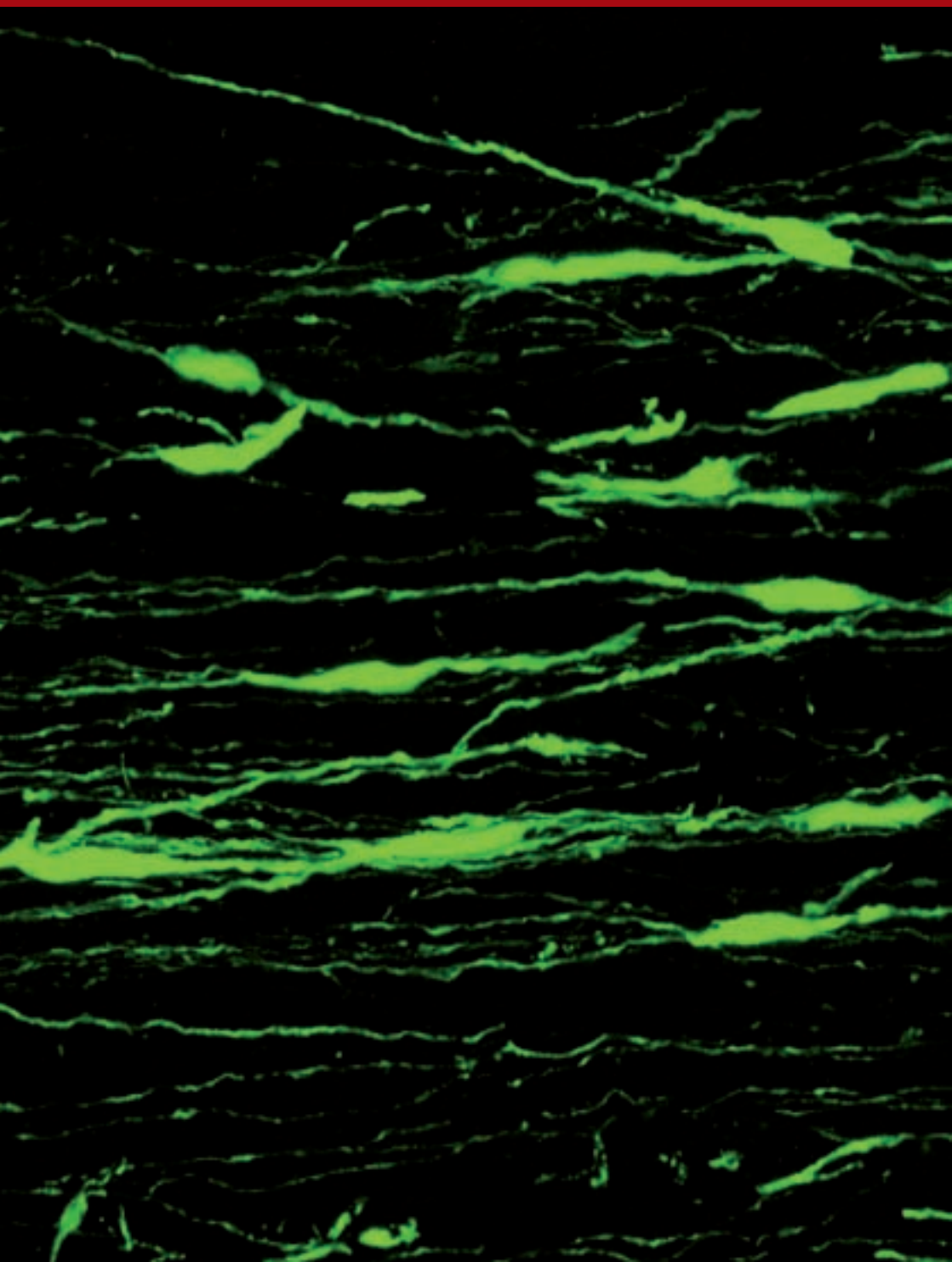


achieved promising results with a T-cell therapy for combating chronic viral infections, which are often a consequence of immunosuppressive treatments following transplantation. Immunologists Petra Reinke and Hans-Dieter Volk from BCRT have conducted clinical pilot studies on regulatory T-cells, whereby immune cells are isolated from patients chronically infected with the Epstein-Barr virus (EBV) and brought into contact with other immune cells *in vitro* before being retransferred to the patient. Another approach is the use of immunotherapy to ameliorate the function of a hyperactive immune system.

The path for regenerative therapies from the laboratory to patients is complicated by numerous regulatory- and health economic hurdles. A crucial point is the validation of regenerative products or processes. Strong evidence for the efficacy and benefits of treatments are required before they can successfully enter the market. They should be effective and also efficient from a health economic point of view. However, evidence for new, individual therapies in regenerative medicine is usually more difficult to produce due to a frequent lack of established and recognized quality indicators and biomarkers. For the approval of medicinal products from human cells, the guidelines of the European Medicines Agency EMEA demand extensive compatibility tests and an examination of the mechanical properties of synthetic tissues – before, during and after transplantation (see Chapter 6).

The BMBF launched a new funding initiative in 2009 to address the respective barriers to innovation. Thereby, consortia from science and industry will help to improve the validation, standardisation and quality assurance of products in regenerative medicine. A consortium of seven research institutions, seven companies and cartilage manufacturers is being funded within the initiative, among others. One sub-project has the goal of testing the resilience and the biomechanical properties of cartilage cell transplants in the laboratory and in animal models. Two sub-projects take in clinical trials in which the application of cartilage replacement tissue is being tested on patients. A fourth sub-project is focused on the transfer of cartilage cell products in medical practical application. A GMP testing laboratory is planned to be established, in which all tests required for the approval of regenerative medical products can be carried out.

## Quality Standards

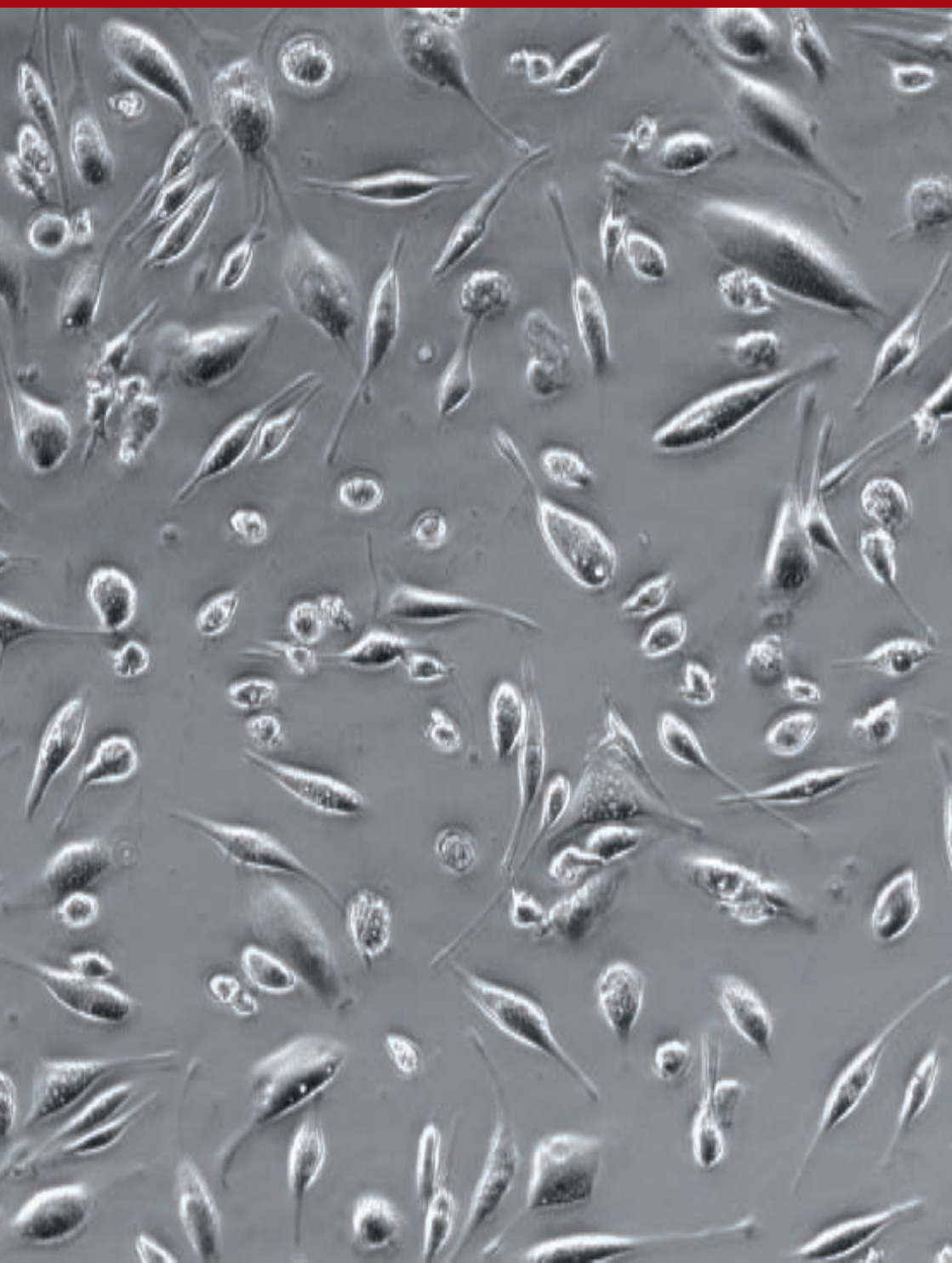




# Legal Framework

In Germany, research and development in the field of regenerative medicine is subject to a variety of regulatory frameworks, at both a national and European level. Because this area is extremely complex, it's impossible to go into detail about all of the relevant laws and regulations here.

The most important frameworks include the following: Embryonenschutzgesetz (Embryo Protection Act), Stammzellgesetz (Stem Cell Act), Gentechnikgesetz (Genetic Engineering Act), Arzneimittelgesetz (German Medicines Act), and Medizinproduktegesetz (Medicinal Products Act). Additionally, the Transfusionsgesetz (German Transfusion Act) is important at the national level, and the Advanced Therapy Regulation is relevant at the EU Level.



# Funding

Germany is at the forefront in international comparison in the field of regenerative technologies and medicines in science and business. The Federal Ministry of Education and Research (BMBF) has been supporting German researchers and companies for decades.

In 2006, a review of the field realized by the consulting company CapGemini was published in the face of huge international investment and the correspondingly high research dynamic. It was determined that investment from the BMBF and the German Research Foundation (DFG), totaling 230 million euros from 1990 until 2006, has created a solid scientific foundation in Germany. What is now required is for findings from basic research and from applied research to be supported during translation into products through the creation of appropriate framework conditions.

To these ends, the creation of translation centers in regenerative medicine is the subject of targeted funding. Seven centers with a variety of emphases have emerged since 2006. These have been equipped by the federal government with more than 230 million euros (see Chapter 2). Added to this is further funding from the federal states and from private funds.

## Translation Centers

Alongside the translation centers, the BMBF is also supporting diverse fields of research within regenerative medicine. From 2000 to 2007, numerous research groups and companies in the field of tissue engineering have been funded with a total of 45 million euros. Projects here relate mainly to the development of biotechnological procedures for tissue engineering, and for hybrid tissue replacement. Other funded projects are occupied with the extraction, cultivation and differentiation of stem cells and other issues in cell biology and developmental biology.

## Tissue Engineering

### Cell-based Therapies

Based on the knowledge of precursor and stem cells, the targeted use of the body's own regenerative potential for therapeutic approaches is coming within reach. To drive forward the application of findings from basic research to the clinic, the development of cell-based therapies in a variety of indication areas has been funded with 30 million euros since 2005. The goal is to smooth the transfer of knowledge towards clinical application through cooperation between basic scientists, clinicians and materials researchers. This is intended to make new treatment options available, especially for economically significant diseases in which current treatment options (such long-term medication or organ transplantation) are associated with serious side effects.

### Multi-and Pluripotent Stem Cells

Moreover, the foundation for the development of new cell-based regenerative therapies is the availability of stem cell sources that are suited to requirements, and which are ethically and legally defensible. For this reason, there is considerable interest in the development of procedures for the extraction of multi/pluripotent human cells that are compatible with the protection of human embryos. A BMBF-funded initiative with an emphasis on multi/pluripotent stem cells, and equipped with funding of around 9 million euros, has been underway since 2008.

### Regenerative Technologies

To address barriers to innovation in the field of regenerative medicine in clinical trials and in the approval procedure, the BMBF has also provided support since 2009 for consortia developing new validation and standardization procedures for products in regenerative medi-



cine, and which are establishing innovative forms of cooperation between research and industry. The funding volume for this initiative comes to 15 million euros.

The field of regenerative medicine places a particularly strong emphasis on transdisciplinary approaches. This is true for technological and clinical developments, and equally for the transfer of new scientific techniques and understanding into medical application. In order to implement these transdisciplinary approaches, the BMBF is supporting international cooperation between German scientists and world-leading experts in the field. Accordingly, bilateral agreements in the field of regenerative medicine are being pursued with research funding agencies in the United States. Since October 2009, a Memorandum of Understanding has been in place with the Californian Institute for Regenerative Medicine (CIRM), enabling German researchers or research institutions to participate in calls from the CIRM in the framework of US-German cooperations. Conversely, it will be possible for American researchers and research institutions to participate in German calls in the context of German-US cooperations. Thereby, the BMBF provides funding only for the German contribution within a partnership. Eligible to apply are small and medium-sized businesses, clinics specializing in regenerative therapies, and research institutions receiving joint basic funding from federal and state governments. A total of four calls are planned for 2010 for a variety of key topics within regenerative medicine. Future cooperation partners are being planned alongside the CIRM.

### International Cooperation





### About Project Management Juelich

As one of Germany's leading project management organizations, Project Management Juelich (PTJ) is a partner for researchers, industry representatives, and policy-makers. With capacities in research and innovation management, PTJ assists contractors at federal and federal-state level and in the European Commission to realize their research targets. PTJ thus serves as an important interface – to make Germany a competitive research and innovation location in a common European Research Area.

In 1974, the Federal Minister for Research initiated the foundation of Project Management Juelich. The original brief was to implement the Federal Government's Energy Research Program. Today, around 340 staff are active in ten fields of work, among others biotechnology, covering a broad thematic array. In the field of regenerative medicine, PTJ supports the implementation of funding initiatives from the Federal Ministry of Education and Research.

### Contact:

Project Management Juelich  
Forschungszentrum Juelich GmbH  
Division Biology (PtJ-BIO 4)  
52425 Juelich

Dr. Marion Wehner  
m.wehner@fz-juelich.de  
phone: +49 2461-61-4809; -8786

Dr. Bülent Genç  
b.genc@fz-juelich.de  
phone.: 02461 61-5265

[www.fz-juelich.de/ptj/biotechnology](http://www.fz-juelich.de/ptj/biotechnology)

# biotechnologie.de

## the information portal

The information portal biotechnologie.de, an initiative of the Federal Ministry of Education and Research, has been active since 2006. Here, biotechnology in Germany – including regenerative medicine – is represented as one of the most innovative fields in science and business. Covering research, funding, business, legal basis, studies and more, biotechnologie.de offers a wealth of data and knowledge. Regular researcher portraits provide background on the influences, motivations, goals and careers of German scientists in biotechnology, and examples of BMBF funding initiatives for biotechnology are also outlined.

About  
[biotechnologie.de](http://biotechnologie.de)

The core of the information portal is a continually up-to-date database that provides an invaluable overview of the biotechnology business and research landscape in Germany, and which is searchable with a wide range of criteria.

The website is intended not only for the professional public, but also for anyone interested in biotechnology.

### Contact:

BIOCOM Projectmanagement  
Brunnenstraße 128  
13355 Berlin

[info@biotechnologie.de](mailto:info@biotechnologie.de)  
phone: +49 30 264 921 60

[www.biotechnologie.de](http://www.biotechnologie.de)





## Picture credits

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Page 4	Muscle model Source: Georg Duda, BCRT	Page 30	Model for the tissue engineering of heart valves using the injection moulding technique; Source: Stefan Jockenhövel, RWTH Aachen
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