The basis of regenerative medicine

Whether for direct cell and tissue replacement or as a support for the body’s self-healing powers – stem cells are a key resource for novel therapies. Rapid technological advances have already enabled a number of stem cell treatments to benefit patients. However, the great majority of therapeutic approaches currently under development are still a long way from the clinic. A new generation of translational centers has recently been established in Germany to speed developments in regenerative medicine and a dedicated GSCN working group now aims to pool the expertise and experience necessary to move new ideas into new applications.

H ealing with cells – that is the central concept of regenerative medicine. The translation of research findings out of the stem cell laboratories and into clinical practice has caught the public imagination and raised patient expectations. However, experience has shown that the path to a scientifically sound and sufficiently proven cell therapy is frequently long and laborious. To date, hematopoietic stem cell transplantation for the treatment of blood cancers is still the only stem cell therapy in routine and widespread clinical use. Even here, the procedure remains strongly dependent on the availability of suitable donors and, despite decades of experience, still carries the risk of dangerous side effects. A major technical hurdle also continues to limit progress in this area: Like many other somatic stem cells, blood stem cells are difficult to expand in the laboratory.

iPS cells as game changers

Against this background, the hopes and aspirations of biomedical scientists in Germany and around the world are being pinned increasingly on the spectacular results emerging from cellular reprogramming and in particular on the isolation of induced pluripotent stem cells (iPS cells). “We certainly regard human iPS technology as a breakthrough,” says Ulrich Martin from the Leibniz Research Laboratories for Biotechnology and Artificial Organs (LEBAO) at the Hannover Medical School. Martin is one of the initiators of the GSCN working group ‘Stem cells in regenerative therapies’. Aided by iPS technology, researchers in Germany now have the means to produce pluripotent cells, cultivate them in large quantities and use them to derive specialized cell types. “It is nevertheless clear that clinicians around the world are at the very beginning of the learning curve with regard to iPS-based cell therapies” says Martin. The first clinical trials with iPS-derived retinal pigment epithelial cells are due to begin in Japan in 2014. In Germany, the majority of research groups are currently focusing on alternative applications for pluripotent stem cells, primarily drug screening and the development of culture models to enable closer investigations of disease processes (see the separate chapter on page 34 ff). Ulrich Martin, however, has by no means lost sight of the therapeutic applications. His team specializes in the regeneration of diseased or injured hearts. In Hannover, researchers are investigating whether iPS-derived cells can be transplanted into lesioned myocardial muscle, and have already gathered encouraging data in animal models. Another possible application for these cultured heart muscle cells is as a starting material for the production of bioartificial tissue constructs.

Clarifying safety aspects

Stem cell researcher Martin stresses that there are still a great many challenges to overcome. Although new purification techniques make it possible to exclude almost entirely contamination of cell material with undifferentiated iPS cells, “Genetic mutations in the iPS cells represent a major unresolved issue,” says Martin. Although these kinds of mutations could arise during cell culture, the major threat may be posed by those already present in the cells used for reprogramming. The worry here is that granting a new lease of life to mutated cells may lead to a higher incidence of malignancy. “The quest for safer cell sources or logistical solutions such as the establishment of cell banks is going to occupy us intensively in the future,” says Martin. Among his other activities, Martin is involved in the development of clinically safer cell products from umbilical cord blood, and of new tools for the correction of genetic defects in patient-specific stem cells.

Spotlight on somatic stem cells

As a consequence of the ethical and legal climate and the resulting funding policies, biomedical researchers in Germany have traditionally concentrated more on the therapeutic potential of somatic stem cells. Michael Cross, who heads the hematological stem cell laboratory at the University Hospital in Leipzig, is co-initiator of the GSCN working group. Cross sees a continuing increase in national activity in this area most noticeably with respect to mesenchymal stem cells (MSCs). “At the first GSCN annual conference, a third of the poster contributions for regenerative therapies were from this area,” says Cross. MSCs are popular not only because they can develop into cartilage, bone, muscle and adipose tissue, but also because they mitigate inflammatory and immune responses and can support the development of blood progenitor cells in the bone marrow. Germany is also strong in the hematopoietic stem cell field, with extensive experience and healthy cooperation between specialized clinics,

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Bioartificial cardiac tissue (BCT) in a bioreactor
The REBIRTH Cluster of Excellence

From Regenerative Biology to Reconstructive Therapy

REBIRTH has, under the nationwide Excellence Initiative, been funded as a cluster of excellence since 2006. Its aim is to develop innovative therapies for the heart, liver, lungs and blood, and to translate these into clinical use. This involves collaboration – in Hannover and at participating partner institutions – between physicians, physicists, chemists, biologists, engineers, legal professionals and ethicists; the main research priorities being stem cell biology, the reprogramming of cells for cell therapy, disease models and tissue engineering. The review process prior to the second funding period showed that REBIRTH has successfully established itself as an internationally renowned centre for regenerative medicine.

Participating Partners:
- Hannover Medical School
- Leibniz University of Hannover
- Hannover Laser Centre
- University of Veterinary Medicine Hannover, Foundation
- Helmholtz Centre for Infection Research Braunschweig
- Max Planck Institute for Molecular Biomedicine, Münster
- Institute of Farm Animal Genetics, Friedrich Loeffler Institute, Mariensee
- Fraunhofer Institute of Toxicology and Experimental Medicine, Hannover

In Hannover, the DFG-financed Cluster of Excellence REBIRTH, brings together a total of seven local research institutions in an initiative that is coordinated by the Hannover Medical School and that focuses primarily on diseases of the blood, heart, lungs and liver. The Berlin-Brandenburg Center for Regenerative Therapies (BCRT), led by Hans-Dieter Volk, is supported by the BMBF, the federal states of Berlin and Brandenburg, the Berlin University Charité hospital and the Helmholtz Association. Research here is concentrated in four major areas: the immune-, cardiovascular-, nervous- and musculoskeletal-systems. Leipzig is home to the Translational Center for Regenerative Medicine (TRM). This center, which is funded by the BMBF, the State of Saxony and the University of Leipzig, works closely with the Fraunhofer Institute for Cell Therapy and Immunology (IZI). One of the research areas of the TRM is dedicated exclusively to cell therapies, approaching a wide spectrum of degenerative diseases of the nervous system, the skin and the musculoskeletal system. Director of the TRM Leipzig and Fraunhofer IZI is Frank Emmrich, who is also one of the initiators of a GSCN strategic working group on stem cell technologies.

Translational research into cell therapies

Anybody looking for an expert in cell-based therapies in Germany would be wise to head for one of the translation centers for regenerative medicine. These centers place a strong emphasis on interdisciplinarity and combine basic and applied research to establish a scientific platform for the development of future therapies. Their construction has been promoted over the past ten years by the German Federal Ministry of Education and Research (BMBF) and the German Research Foundation (DFG). There are now five major translational centers with a focus on regenerative medicine – in Hannover, Berlin, Dresden, Rostock, and Leipzig. In addition, regional initiatives have led to the establishment of further centres for cell-based therapies in the southern and western regions of Germany including Stuttgart and Tübingen, around Frankfurt am Main and in Würzburg.
A further important location in Saxony is the DFG-funded Center for Regenerative Therapies Dresden (CRTD). Here, studies are underway into the use of stem cell-based therapies for five medical indications: hematological diseases, diabetes, neurodegenerative diseases, bone and cartilage replacement, and cardiovascular diseases. For its part, the Reference and Translation Center for Cardiac Stem Cell Therapy (RTC) in Rostock is focused exclusively on clinical testing of a specific cell therapy for heart disease in the multicenter clinical trial known as “PERFECT”. In this trial, coordinated by Gustav Steinhoff, CD133+ cells from the bone marrow are isolated from cardiac patients during a bypass operation and re-injected into the heart muscle. It is the hope of researchers that once inside the body and secreting a mix of molecules, these cells will boost the regeneration of the affected area. The Health Region REGINA between Stuttgart and Tübingen has also established itself as a translation location for cell-based therapies. The LOEWE Center for Cell and Gene Therapy in Frankfurt, founded as part of a regional Excellence Initiative in Hessen, develops innovative therapies for clinical application, particular for cardiovascular and hematological diseases. In Munich, numerous university clinics and the local Helmholtz Center are working on the development of cell therapies. A new Fraunhofer Translation Center for medical products and cell-based regenerative therapies is in the planning stages in Würzburg. Finally, the region of North Rhine-Westphalia is also emerging as a powerhouse for research into the technologies and cell sources for the stem cell therapies of the future, with activities in Aachen, Bochum, Bonn, Düsseldorf, Cologne and Münster.

Raising awareness of regulatory issues

The GSCN working group provides an opportunity for experts and young scientists from the various research centers to benefit from each other’s experience, expertise and resources, says Martin. This forum should also encourage new collaborations at the national and international level. Some researchers are already involved in EU networks or Ministry-funded collaborations with stem cell researchers in the United States developing strategies for future cell-based treatments. There is also the matter of raising awareness of the many studies and approval issues that lie ahead: “It is important to be prepared for a lengthy process and to deal with approval-relevant issues in a timely manner,” stresses Martin. To address such questions, the GSCN has established a strategic working group ‘Clinical trials and regulatory affairs’: Initiators are Berlin-based researchers Hans-Dieter Volk and Andreas Kurtz, as well as Torsten Tonn from the medical faculty of the TU Dresden.

Generation of induced pluripotent stem (iPS) cells (see page 18 ff.) and their application in regenerative therapies, disease models and drug development.

**Berlin-Brandenburg Center for Regenerative Therapies (BCRT)**

The Berlin-Brandenburg Center for Regenerative Therapies (BCRT) is an interdisciplinary translational center with the goal of enhancing endogenous regeneration by cells, biomaterials, and factors which can be used to develop and implement innovative therapies and products. At the BCRT clinicians and researchers are working closely together on a personalized medicine that depends on the early recognition of patients’ individual healing potential. The primary focus of the BCRT is on diseases of the immune system, the musculoskeletal system, the cardiovascular system and the kidney for which currently only unsatisfactory treatment options are available. Early cooperation with industry, health insurers and regulatory authorities as well as other external partners boosts the chances of exploiting new methods and provides access to flexible financing options.

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Text: Philipp Graf

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