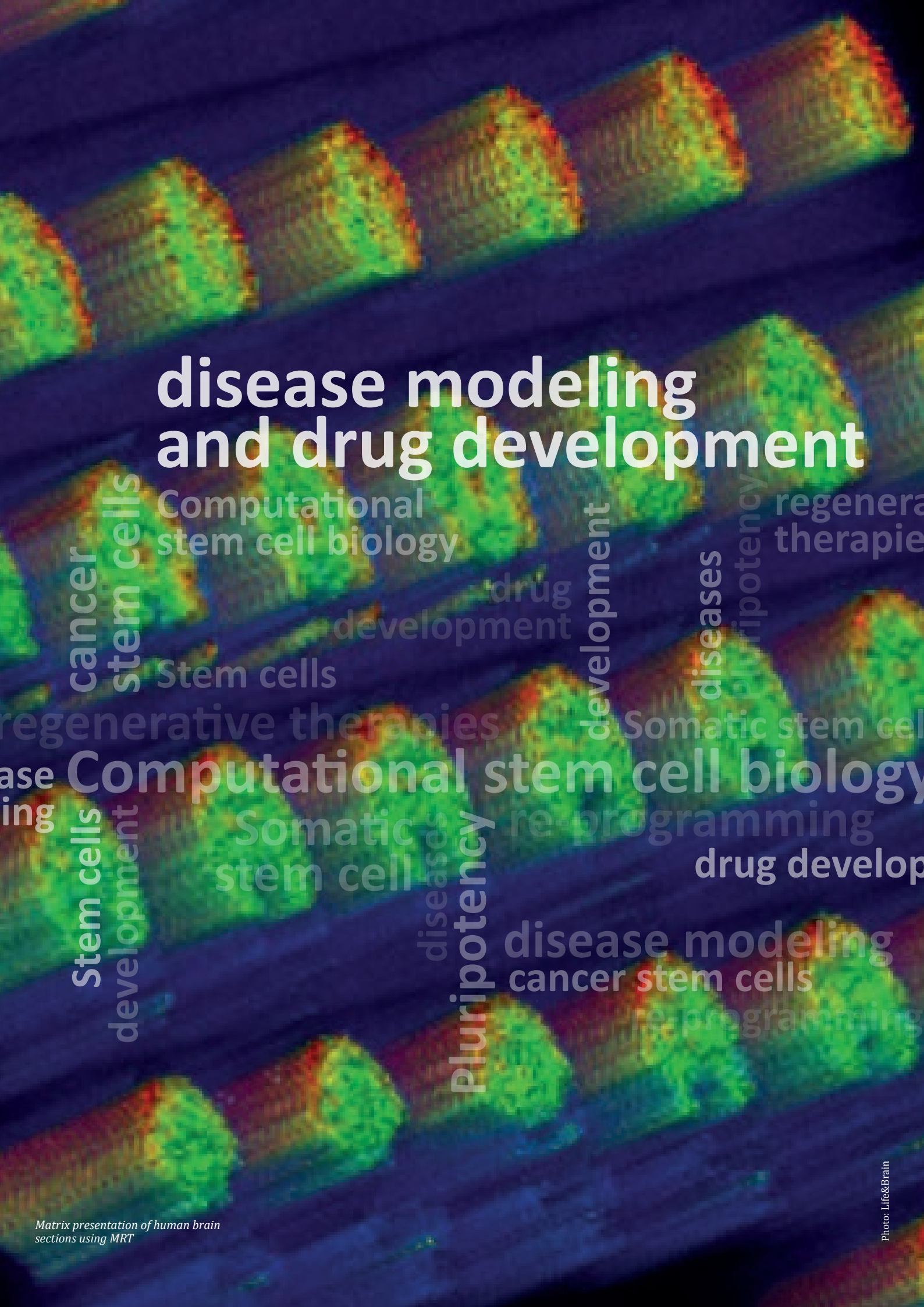


Matrix presentation of human brain sections using MRT

Photo: Life&Brain

Stem cells in disease modeling & drug development

Personalized medicine in the Petri dish

The increasing availability of pluripotent stem cells is set to change the face of health research. In human cell systems, for example, they have already greatly advanced the study of the molecular causes of disease, and cell models or miniature organs in the culture dish are regarded as important tools for expediting toxicological testing and drug discovery in the pharmaceutical industry. German stem cell researchers contribute significantly to this global development towards the establishment of personalized medicine.

Public awareness of stem cells appears to be focused in particular on their application in regenerative therapies. For the most part, however, such treatments require an extremely lengthy development process and take a long time to reach patients. Nonetheless, the first major applications to use pluripotent stem cells promise to become reality in the foreseeable future – a prospect of which many experts and even Nobel Prize winner Shinya Yamanaka are convinced. In this case, it is in the form of a culture dish-based cellular disease model and the subsequent possibilities for drug screening in the pharma industry.

The modern technologies now emerging from stem cell laboratories are opening up new means of exploring the molecular causes of diseases in areas previously lacking direct access to cell material. "These include diseases of the nervous system, the heart or insulin-producing cells in the pancreas," says Oliver Brüstle from the Institute of Reconstructive Neurobiology at the University of Bonn. The GSCN founding president is also one of the initiators of the scientific working group "Stem cells in disease modeling & drug development".

Patient genomes captured in cells

This development has been spurred by pioneering advances such as the generation of induced pluripotent stem (iPS) cells and the findings that have emerged from the field of direct programming. The advantage of reprogramming is that it enables the propagation of patient cells in a Petri dish. In later steps, these are converted into cell types that are relevant for the disease in question (see graphic on page 33). These cells, which carry the genome of a patient, open up new perspectives into the molecular causes of diseases. For the first time, cell researchers have the possibility of developing patient-specific cell models in an 'authentic' human background. These cells are useful both for the observation of disease-causing mechanisms and for the study of the effects of specific active substances. Stem cell research is thus set to bring about major advancements in the emerging treatment concept of 'personalized medicine'.

Stem cells for high-throughput screening

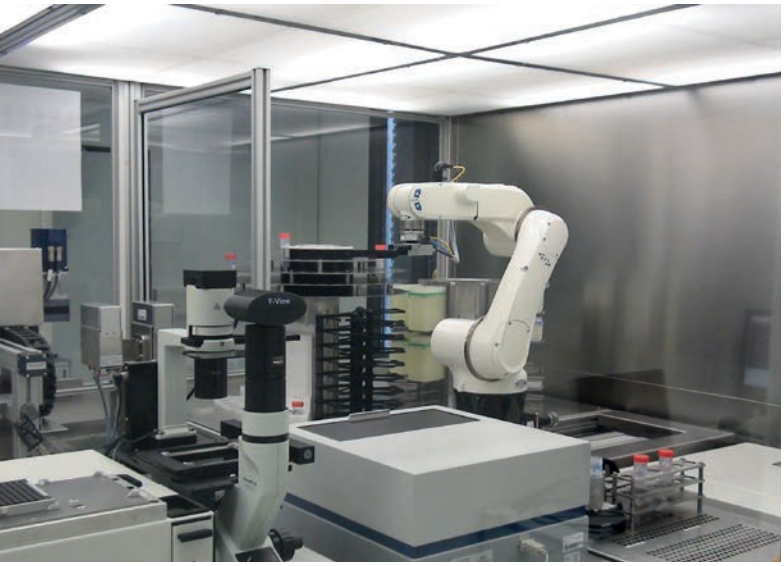
Other technological breakthroughs are opening up entirely new possibilities for the industrial application of stem cells – for the pharma industry, the ability to produce defined human cell types in large quantities is a powerful new premise in the search for novel drugs. Also in pre-clinical toxicological assessments, mass-produced human cell cultures carry great promise as a tool for the minimization of animal testing. At the same time, they make the tests more 'human-specific'.

Pharma industry: looking on with interest

The iPS revolution has even brought about a change in thinking in the pharma industry, where attitudes towards stem cells were previously extremely hesitant. Today, the majority of large companies have greatly expanded their research activities in the field. This growth in interest is also reflected in the cooperation projects currently being pursued by the European Innovative Medicines Initiative (IMI). In the shape of StemBANCC and EBiSC, there are two large consortia providing a base for collaborations between pharmaceutical companies and European research institutions. StemBANCC, which launched in 2013 with a budget of almost €55 million, is working to produce 1,500 human iPS cell lines, in particular for neurodegenerative diseases and diabetes. In the framework of EBiSC, the European Union and partners are contributing €35 million for the construction of a major European iPS cell bank and the cataloguing of over 10,000 patient-specific cell lines. Both consortia include the participation of German stem cell researchers and research institutions.

Research landscape for disease models

Among these is a team of neurogeneticists that is headed by Christine Klein from the University Hospital in Lübeck and which is specialized in the research of hereditary forms of specific neurodegenerative diseases, in particular Parkinson's. In the StemBANCC project, they are coordinating the establishment of a sample bank of skin samples from 500 Parkinson's patients from across Europe. To gain a clearer picture of the basic mechanisms of Parkinson's disease, the researchers are working to draw comparisons between iPS cells from patients and healthy cells and thereby shed light on the mechanisms that promote cell death.



Robot arm in the StemCellFactory

At the Institute of Reconstructive Neurobiology at the University of Bonn, Philipp Koch – a member of Oliver Brüstle's team – has developed an important cellular tool for the development of disease models. Here, the researchers are using human embryonic stem (ES) cells to derive neural stem cells, also known as lt-NES cells. With standardized protocols, these multipotent cells can be used to quickly and reliably generate a range of defined cell types of the central nervous system. Likewise, lt-NES cells can be derived from iPS cells. "This provides us with a path for patient-specific disease models," explains Brüstle. The Bonn-based scientists have already employed this approach to elucidate the pathogenic mechanisms in Machado-Joseph disease. Moreover, aided by neurons from Alzheimer's patients, they have demonstrated that such cell systems can assist in predictions on the efficacy of drugs.

Intensive work at German laboratories

Numerous researchers in Germany are already utilizing patient-specific cell models to place neurodegenerative diseases under far closer scrutiny than was previously possible. One of them is Jared Sterneckert at the Max Planck Institute for Molecular Biomedicine in Münster, who is focusing on the mechanisms of Parkinson's disease. The Bavarian Research Network "ForIPS", which was launched last year, aims at using iPS cell-derived disease models to analyze the pathogenesis of Parkinson's disease in particular. Spokesperson is Erlangen-based neurobiologist Jürgen Winkler. At the university clinic Erlangen, Beate Winner and her group are occupied with the pathogenic mechanisms of Parkinson's and other neurological illnesses.

Stefan Liebau from the Department of Neuroanatomy at the University of Tübingen is employing iPS cells to study motor neuron synapses in patients with muscle weakness. For the future, he is planning to cultivate retinal cells to be used for an improved understanding of the molecular background of degenerative retinal disorders. Suzanne Kadereit from the University of Konstanz is developing cell models that will be employed to test substances for potential neurotoxic effects.

The study of cardiovascular disease in cell cultures is just one of the specialty areas of Karl-Ludwig Laugwitz from the TU Munich's Klinikum rechts der Isar University Hospital. His team is using patient-specific stem cell models to search, among other things, for the molecular background to cardiac arrhythmias. Laugwitz is co-initiator of the GSCN working group. The groups headed by Ulrich Martin at the REBIRTH Cluster of Excellence at the Medical School Hannover (MHH) and Jürgen Hescheler at the University of Cologne are scrutinizing iPS cell-derived heart muscle cells for use in pharmacological testing. The working group of pharmacologist Thomas Eschenhagen from the University Medical Center Hamburg-Eppendorf are developing similar heart muscle models for the testing of individual genetic defects and therapies. The long-term objective is the development of an automated process to assist in predictions about individual susceptibility to heart failure and to facilitate treatment decisions.

At REBIRTH/MHH, Tobias Cantz is concentrating on diseases of the liver. Cantz, who heads a Hannover-based group of Münster's Max Planck Institute for Molecular Biomedicine, is using iPS technology to produce patient-specific hepatocytes for the detailed study of the molecular processes of metabolic liver diseases.

Photo: Life&Brain

Institute of Reconstructive Neurobiology

From disease modeling to stem cell therapies

The Institute of Reconstructive Neurobiology at the University of Bonn Medical Centre focuses on the use of pluripotent stem cells for the study and treatment of neurological disorders. Based on a broad technology portfolio including cell reprogramming, neural differentiation, direct cell fate conversion, stem cell industrialization and neurotransplantation, the Institute develops stem cell-based model systems for disease-related research and drug development as well as novel cell therapy regimens. It closely interacts with LIFE&BRAIN GmbH, a translational hub of the University of Bonn providing stem cell products and services for pharma, biotech and academia.

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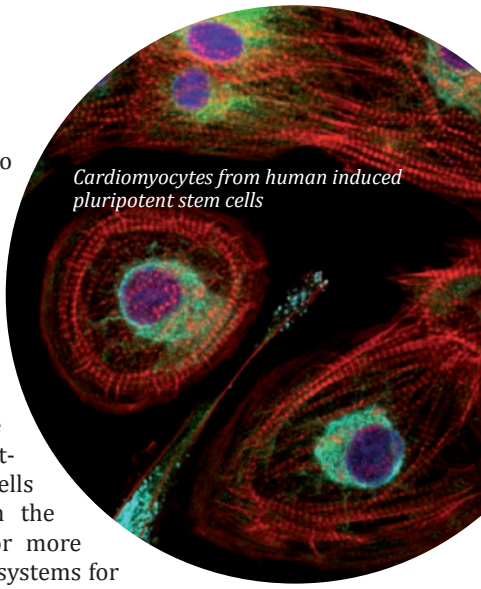

Cardiomyocytes from human induced pluripotent stem cells

Photo: TU Munich/Alessandra Moretti und Klar-Ludwig Laugwitz

Alongside the study of disease in the culture dish, a further important venture of Oliver Brüstle and his team in Bonn is the manufacture of cell products and the industrial-scale testing of active substances. In cooperation with the Fraunhofer Institute for Production Technology IPT and RWTH Aachen, a manufacturing system has recently been implemented at the LIFE&BRAIN research center. It enables the automated production of iPS cells and their differentiation into neural cells or cardiomyocytes. Further research institutes and companies based in North Rhine-Westphalia also participate in the joint project. "Our StemCellFactory is a fully automated production line for iPS cells and their derivatives," says Brüstle. The industrial application of stem cells in compound screening also requires new methods of high-throughput imaging, such as those being developed by Sabrina Desbordes at the Institute of Developmental Genetics of the Helmholtz Center Munich.

Boosting translation

This compact overview only partly reflects the diverse research activities underway in Germany in this field. Today, the GSCN working group is involved heavily with pooling and highlighting this national expertise. "We want to establish a research map that will serve as guidance for scientists but also for interested biotech- and pharmaceutical companies, and thereby improve interexchange between the various stakeholders," says Brüstle. Numerous German pharmaceutical companies have already signaled their interest: "The opportunity to gain patient- and disease-specific stem cells has raised great hopes in the pharmaceutical industry for more predictive and efficient cell systems for drug development," says Ralf Heilker, who works in the Department of Lead Structure Identification at Boehringer Ingelheim's Biberach site.

Brüstle, who is in no doubt that stem cell-based disease models will play a key role in future drug development, emphasizes the importance of forging early alliances with biotech and pharma for the speedy transfer of stem cell research into the healthcare industry.

Text: Philipp Graf