Stem cell-based drug screening

On the hunt for new drugs

Reprogramming, genome editing and robotics: a mixture of powerful stem cell technologies is fundamentally changing the way drugs are developed. After years of taking a "wait and see" stance, the pharmaceutical industry is now making more and more use of cell-based disease models to accelerate the search for new drugs and improve the chances of success. The first substances identified with the help of pluripotent stem cells are already being tested in clinical trials. New translation centers are now implementing findings from German laboratories in stem cell-based drug screening. And two major European projects are working together to set up a giant stem cell bank.

It is less than ten years since Japanese scientist Shinya Yamanaka first converted somatic cells into induced pluripotent stem cells (iPS cells). Even then, Yamanaka – who was subsequently awarded the Nobel Prize – and many other researchers were convinced that the first major application of the revolutionary reprogramming technique would be drugs based on cell models.

For pharmaceutical researchers, the refinement of the iPS technique opened up a promising new way of searching for and testing new drugs. In previous years, the pharmaceutical industry had suffered too many costly setbacks. Drugs that had appeared promising failed in the late stages of clinical development, often because the results of experiments with immortalized cell lines or on animals proved insufficiently transferable to patients.

The iPS technique gives biomedical experts direct access to "authentic" human cell material that they have never had before. In addition, patient-specific cells or even simple miniature organs can be produced, enabling diseases to be modelled in the Petri dish. New tools from molecular biology – in particular genome editing – have vastly increased the options open to stem cell researchers. With designer nucleases such as the now popular CRISPR/Cas9 system, the stem cells' genetic material can be modified in precise ways. This means that the cells of the disease models can be genetically tailored in the laboratory. The possible functions of gene variants that have already been linked to the emergence of disease through genome analysis can now be systematically examined in a cell-based model in the Petri dish. Producing corresponding control cells further increases the informative value of the results.

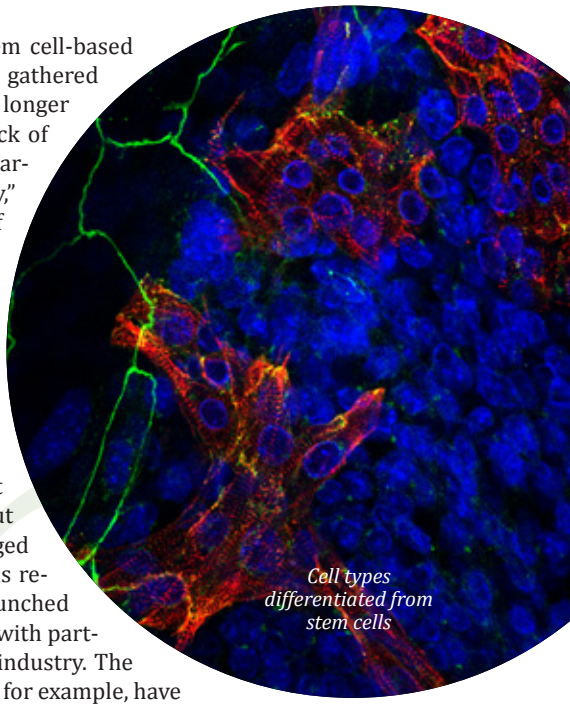
A new era in pharmaceutical research

In the early days, pharmaceutical research tended to focus on stem cell-based toxicity tests; now, however, drug development is also gaining in importance. Worldwide, the first clinical studies are getting under way on substances that have emerged from stem cell-based screening. The major pharmaceutical companies have their sights set on neurodegenerative and psychiatric disorders in particular:

- GlaxoSmithKline has started a Phase II clinical trial of the drug Retigabine involving 192 patients with amyotrophic lateral sclerosis (ALS). IPS-based disease models have shown that the drug helps reduce the excitability of damaged motor neurons.
- Roche is testing the drug known as RG7800 on patients with spinal muscular atrophy (SMA) in a Phase II trial; the substance has been validated in an iPS-based model.
- Bristol-Myers Squibb (BMS) has commenced two Phase I trials of a tau-specific antibody as a treatment for Alzheimer's. The drug BMS-986168 originated with iPierian, a start-up acquired by BMS in 2014.
- Novartis is using drug screening on iPS-based cell models to search for treatments for autism; according to media reports it is planning a clinical trial with a promising candidate.

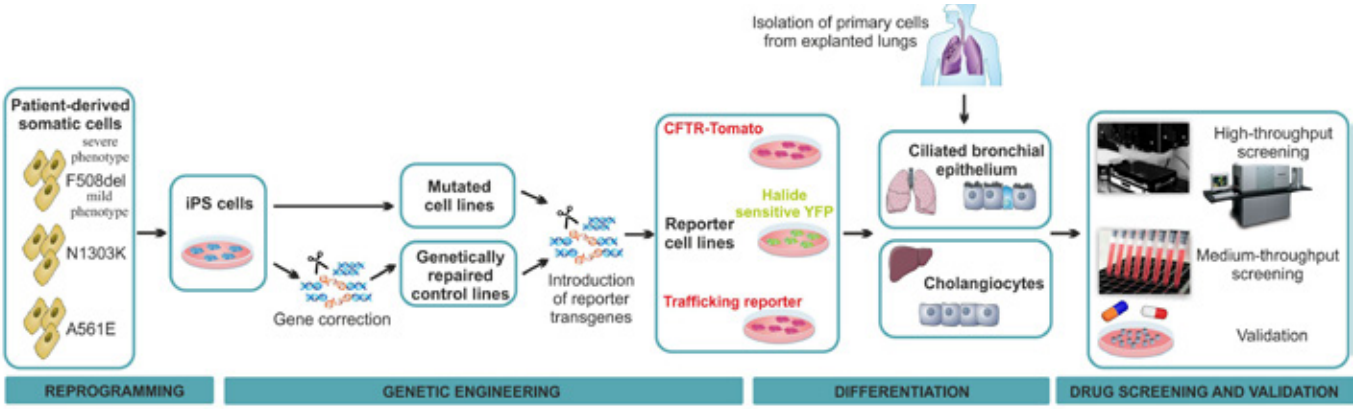
New translation centers set up

In Germany, too, stem cell-based drug screening has gathered pace. "We can no longer complain about a lack of interest from the pharmaceutical industry," says Oliver Brüstle of the Institute of Reconstructive Neurobiology in Bonn. "Five years ago the situation was completely different: then, the pharmaceutical sector was very hesitant about our ideas, but that has now changed radically." The shift is reflected in newly launched translation projects with partners in science and industry. The researchers in Bonn, for example, have



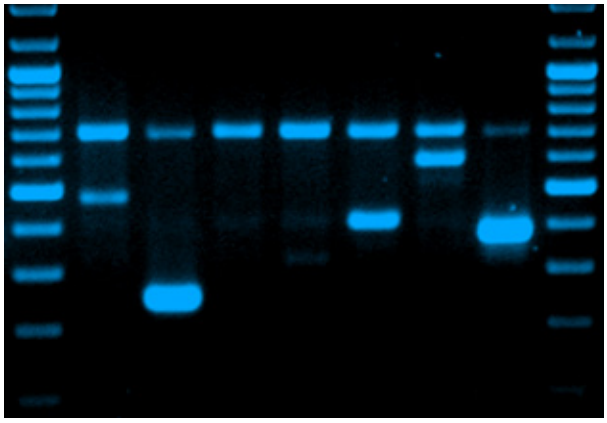
Cell types differentiated from stem cells

Photo: MDC / Chen Chen



From stem cells to drug screening (example for cystic fibrosis mutations)

forged an alliance with the Franco-German translation center KSILINK in Strasbourg: using artificially produced brain cells they will test potential drugs for the treatment of neurodegenerative diseases. KSILINK is a public-private partnership funded by the French government and pharmaceutical company Sanofi. "The aim is for KSILINK to become a bi-national platform for stem cell-based drug development," says Brüstle. In his view, it is not only the European character of the alliance that makes it an interesting concept. "It promotes direct collaboration between applied stem cell research and the pharmaceutical industry and thus speeds up drug development," he says. The researchers in Bonn will produce neural cells for various screening projects and send them to Strasbourg.



The collaboration came about partly because Brüstle's team at the Bonn translation center LIFE & BRAIN turned their attention at an early stage to the issues of standardization and automation that are crucial for the pharmaceutical industry. "This involved lengthy and sometimes tedious work," says Brüstle. "But it enabled us to find a common language." Another flagship automation project is the StemCellFactory. This robotic production line built at LIFE & BRAIN with support from the state of North Rhine-Westphalia is a fully automated system for producing iPS cells that will also manage their maturation into neural cells. The system is intended for use in large-scale centers and cell banks; biobanks have already signaled their interest in the machine. "The StemCellFactory is currently a prototype and not yet in series production. Further improvements to the system are under way, and we want to incorporate other components such as genome editing," says Brüstle.

Graphic: MHH / Ulrich Martin; Photo: MDC / Jochen Meier

Institute of Reconstructive Neurobiology

From disease modeling to stem cell therapies

Institute of Reconstructive Neurobiology

universitätbonn

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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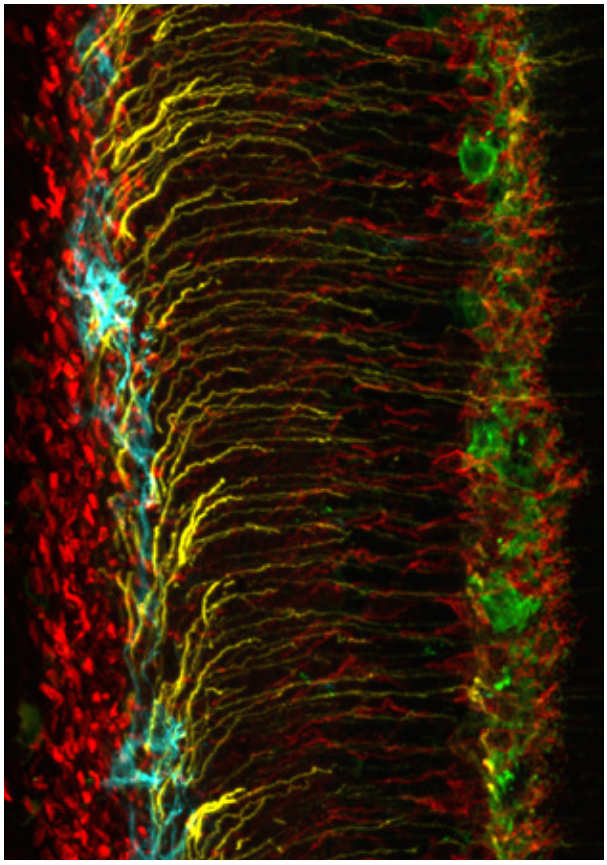
CARE comes to Munich

Another publicly funded translation center for drug development based on iPS cells is to be set up in Munich – the Center for Advanced Regenerative Engineering, or CARE. The Bavarian state parliament approved start-up funding for the center in late 2015. An initial sum of €15 million will be pumped into the development of CARE over the next three years, "CARE is likely to be set up on the Biotech Campus in Martinsried," says Schöler. The center is due to start work in January 2017 with the aim of using iPS cell technology and patient-specific disease models to develop high-throughput assay formats for drug research. "We plan to focus mainly on neurodegenerative diseases. In the search for new therapeutic approaches we are in principle prepared to investigate all types of cells and diseases," says Schöler. CARE is to become a center of excellence for regenerative medicine – a place where drug research companies of all sizes from large to small can get actively involved. "Many companies have already announced their interest," reports Schöler. Science Manager Ulrich Gerth will use 2016 to set up the institute and recruit the first cooperation partners. CARE will strengthen the existing biomedical regional networks in Bavaria, which include m4, the top-level cluster for personalized medicine supported by the German Ministry of Education and Research (BMBF), and forIPS, the Bavarian Research Network Induced Pluripotent Stem Cells. Through these efforts, CARE will also enhance international visibility.



Immunohistochemical staining of an adult mouse retina section

Photo: CRTD / Ruslan Rust

New drugs for cystic fibrosis

The EU is also supporting translational approaches to stem cell-based drug screening – for example in the ERA-Net initiative E-rare, in which European research networks are developing treatments for rare diseases. One of these projects, INSTINCT, was launched at the end of 2015 and is being coordinated by Ulrich Martin of the Leibniz Research Laboratories for Biotechnology and Artificial Organs (LEBAO) at Hannover Medical School (MHH). "We are looking for new drugs to treat cystic fibrosis using patient-specific iPS cell lines," says Martin, who is also the current GSCN President. Cystic fibrosis is a metabolic disorder caused by a defect in the genetic blueprint for the ion channel regulator CFTR. Although the first drugs have recently come on the market, only five percent of patients are benefitting from this causal therapy. Their patient-specific stem cells are being matured into epithelial lung cells in the Petri dish by Martin's team of researchers. "We have produced cell lines with mutations in the CFTR gene that had not previously been widely studied. Now that we have reporter

Heidelberg Institute for Stem Cell Technology and Experimental Medicine

HI-STEM gGmbH

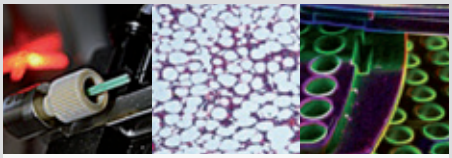
HI-STEM gGmbH is a non-profit public-private partnership between the German Cancer Research Center (DKFZ) and the Dietmar Hopp Foundation (DHS).

Located within the DKFZ in Heidelberg, HI-STEM performs cutting-edge research on stem cells with the aim of translating these results into novel clinical applications. This includes the development of novel diagnostic tools and innovative therapies to monitor and target leukemic and solid tumor stem cells as well as metastatic disease.

Professor Dr. Andreas Trumpp and four Junior Group Leaders direct an international research team of more than fifty employees.

The HI-STEM Research Groups:

- Hematopoietic and Leukemic Stem Cells (A. Trumpp)
- Experimental Hematology (M. Milsom)
- Stress induced activation of HSCs (M. Essers)
- Cancer Stem Cells and Metastasis (A. Trumpp & M. Spick)
- Metastatic Niches (T. Oskarsson)



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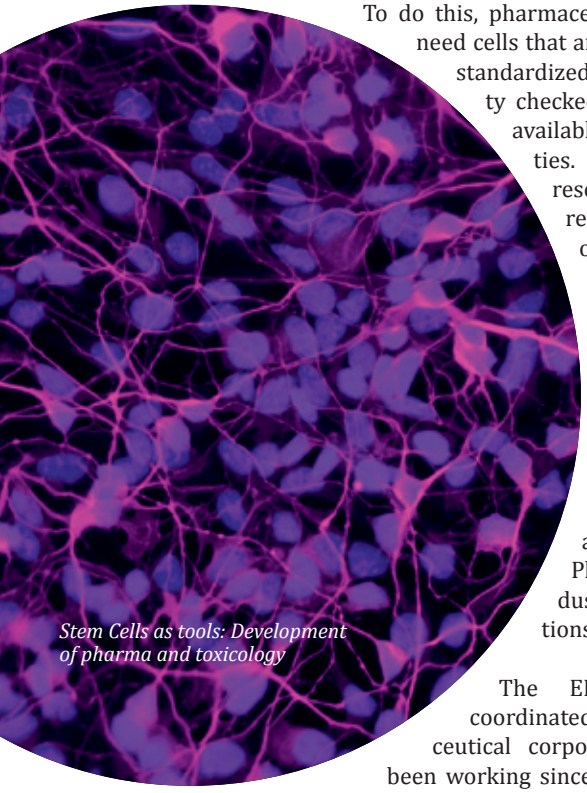
genes we can carry out high-throughput screening of drug libraries." The research partners are a very international group, with representatives from Italy, Portugal, the Netherlands and Canada. Interesting substances will be taken as far as the pre-clinical phase of drug development.

Two IMI consortia on iPS cells

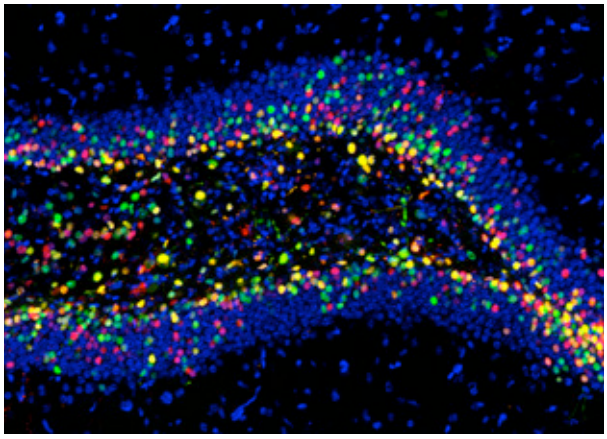
Stem cell-based techniques not only help in the identification of new drugs: In pharmaceutical research, they have also become important tools in the lead validation and optimization of drug candidates found through conventional means.



Stem Cells as tools: Development of pharma and toxicology

To do this, pharmaceutical researchers need cells that are produced under standardized conditions, quality checked, catalogued, and available in large quantities. Central European resources are currently being developed in two large consortia as part of the Innovative Medicines Initiative (IMI). IMI is a public-private partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA).

The EBiSC consortium coordinated by the pharmaceutical corporation Pfizer has been working since 2014 on producing well-characterized iPS cell lines and systematically archiving them in a non-commercial bank. The central biobank is located in Cambridge, UK. A mirror bank that will store a complete equivalent of the EBiSC collection is being created in Sulzbach in the Saarland region of Germany. EBiSC, which has a budget of €35 million, is a consortium of 26 organizations, including seven German partners. The StemBANCC consortium, with a budget of €55 million, was launched in 2012. It is coordinated by Swiss pharmaceutical company Roche. Nine of the 35 partners are from Germany. The consortium partners have an ambitious target: to collect skin samples from 500 patients and to generate from them 1,500 cell lines that will then also be included in the EBiSC collection. The focus is on neuronal and neurodegenerative disorders and diabetes.



Dentate gyrus (part of the brain structure hippocampus) infected with the human immunodeficiency virus (HIV)

The iPS technology has now acquired an established place in the laboratories of the pharmaceutical industry. Stem cells have become a versatile tool for drug developers, and if the new drug candidates perform well in clinical trials they will play a major role in the medicine of the future.

Text: Philipp Graf

Photos: CRTD / Sara Bragado Alonso, Lara Marone & Ruslan Rust

Fraunhofer Institute for Molecular Biology and applied Ecology IME

Fraunhofer IME

The Fraunhofer IME conducts research in applied life sciences from a molecular level to entire ecosystems. Our interdisciplinary organization and laboratories with most recent equipment including GMP facilities and complex facilities for environmental simulations allow a wide spectrum of research and development services. IME's overarching goal is the development and use of novel technologies for diagnosis and therapy of human and animal disease as well as protection of crop plants and food supplies.
IME has close ties in terms of personnel and areas of work with the Institute of Molecular Biotechnology of the RWTH Aachen University, the Department of Biology and Biotechnology of Plants of the University Münster, the Department of Applied Entomology of the University Gießen and the Institute for Clinical Pharmacology of the Goethe University Frankfurt/Main.

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