Regenerative medicine

Cell therapies on trial

Healing with cells – that is the principle behind regenerative medicine. Stem cells have long been a routine therapeutic agent in some fields, such as leukemia medicine. However, the high hopes harbored in Germany and elsewhere that adult stem cells might prove useful in treating other diseases have rarely been fulfilled. Now, scientists are steadily improving their understanding of how adult stem cells work, with the result that promising applications are currently being tested for safety and efficacy in clinical trials. Increased knowledge and expertise in dealing with pluripotent cells have ushered in a new era in cell replacement therapy. Worldwide, patients with eye diseases, diabetes and myocardial infarction are now being treated with replacement tissue derived from pluripotent stem cells.

Whether for cell and tissue replacement or to support regeneration within the body, stem cells are a promising source of new treatments. But translating laboratory findings into clinical practice is difficult, because cell-based treatments are highly complex and are usually tailored to the individual patient. In addition, the treatments need to meet strict regulatory requirements and production standards. As with other drugs, the safety and efficacy of stem cell-based treatments must also be tested in clinical trials. The clinical trials register *clinicaltrials.gov* contains details of several thousand trials worldwide that involve stem cells. Almost 200 of these are in Europe. The Paul Ehrlich Institute, which is responsible for approving clinical trials in Germany, states that 35 clinical stem cell studies are underway (see interview with Egbert Flory).

In Germany, clinical research into cell-based therapies is being pursued at the translational centers for regenerative medicine, which were set up more than ten years ago by federal and state bodies and the German Research Foundation (DFG). For more information on this, see the 2013/14 GSCN Annual Magazine. The centers include the REBIRTH Cluster of Excellence in Hannover, the Berlin-Brandenburg Center for Regenerative Therapies (BCRT), the TRM in Leipzig, the RTC in Rostock, and the DFG's Center for Regenerative Therapies in Dresden (CRTD). With the establishment of the LOEWE Center for Cell and Gene Therapy (CGT) as part of the state of Hesse's excellence initiative, the Frankfurt am Main area has also become a stronghold of cell therapy research.

Which cell type for which organ?

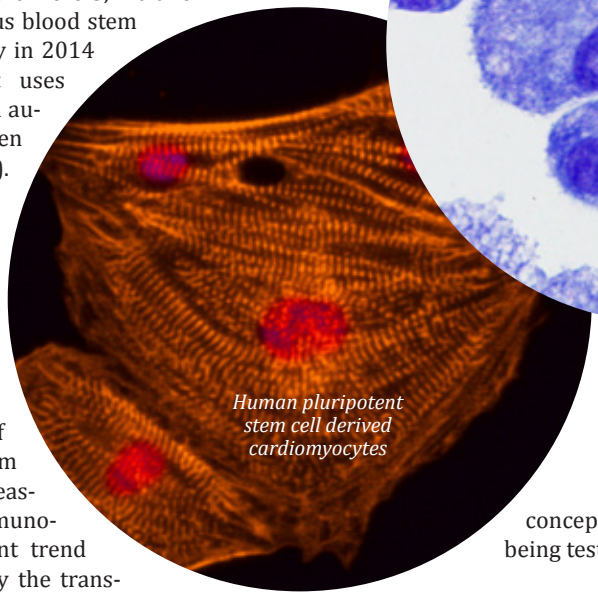
Regenerative medicine utilizes two particular properties of stem cells that promote healing. Firstly, both pluripotent and multipotent stem cells can be used to produce replacement tissue. In a range of disorders that include some eye diseases (e.g. Stargardt's disease), Parkinson's, myocardial infarction and diabetes, specific celltypes are destroyed. These disorders are particularly suited to cell replacement therapy: the hope is that the engineered tissue can replace the lost organ functions and support regeneration. Secondly, stem cells are a sort of "living pharmacy" which emits a cocktail of growth factors and messenger substances that promote regeneration or have a beneficial effect on the immune system. But which cell type is best for which disease? Traditional cell therapies are based on adult stem cells, but a new generation of cell replacement therapies is currently emerging. Preparations based on human embryonic stem cells (ES cells) and induced pluripotent stem cells (iPS cells) are being tested worldwide.

Blood stem cell therapy for leukemia

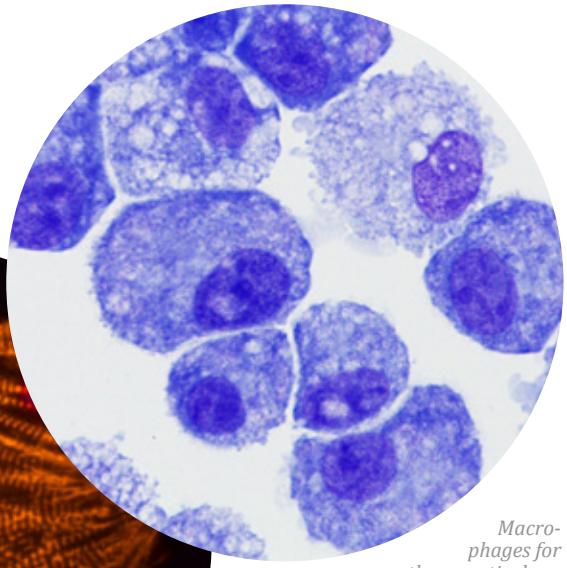
The old hand among stem cell therapies has been around for more than 50 years: blood stem cell transplantation is a firmly established practice in leukemia medicine. The technique uses blood stem cells obtained either from bone marrow donation or by taking peripheral blood stem cells from the patient's blood or that of suitable donors. The more modern blood stem cell transplantation method involves mobilizing the hematopoietic stem cells in the bone marrow with drugs and drawing them into the blood. They can then be extracted and filtered out by means of a type of blood washing in a blood donation process that lasts about five hours. If the cells are introduced into the patient via blood transfusion after chemotherapy, they autonomously settle in the bone marrow niches, then reproduce and re-start the process of hematopoiesis. In time, therefore, a new immune system develops.

"Obtaining stem cells from peripheral blood has greatly simplified the process of donating bloods cells and significantly increased willingness to donate," says Torsten Tonn, Professor of Transfusion Medicine at the Carl Gustav Carus Faculty of Medicine at TU Dresden. In recent years, Tonn has also witnessed a resurgence in bone marrow donation. "In many cases it results in fewer side effects and rejections," says Tonn, who is also Medical Director of the

German Red Cross Blood Donor Service North-East. According to the figures of the German Registry for Stem Cell Transplantation (DRST) there were 3,220 allogeneic and 3,241 autologous blood stem cell transplants in Germany in 2014 (an allogeneic transplant uses stem cells from a donor; an autologous one uses cells taken previously from the patient). Although stem cell therapy is now routine in the treatment of leukemia, it still has risks and side effects, including rejection and infection. Doctors are therefore attempting to refine the concept further and to control the effects of the cell therapy. "Blood stem cell transplantation is increasingly being regarded as immunotherapy, and one important trend here is the move to modify the transplant in specific ways using biotechnology," says Tonn. He goes on to explain that a tailored transplant involves – among other things – filtering out unwanted or disruptive immune cells and increasing the quantity of other cells to support the recipient's immune defenses.



Human pluripotent stem cell derived cardiomyocytes



Macrophages for therapeutical use derived from stem cells

Combined stem cell therapy

In another trend, blood stem cell therapy is being combined with mesenchymal stem/stromal cells (MSCs). The special feature of these adult cell types, which can likewise be obtained from the bone marrow and from other tissue, is that they have immunomodulatory properties and can therefore suppress an overactive immune response in the body. Doctors hope to use the immunosuppressive function of MSCs to tackle a much-feared complication, that of graft-versus-host disease (GvHD), in which the immune cells of the donor transplant attack the recipient's cells, triggering potentially severe immune responses. Promising therapy concepts based on MSCs are currently being tested in numerous clinical trials.

Experimental cell therapies for infarcted hearts

Stem cells in the bone marrow are also being used in the regeneration of infarcted hearts. German researchers are among the pioneers of this experimental stem cell therapy.

With hindsight, the first steps back in 2001 were not something to be so proud of. At that time, Bodo-Eckehard Strauer, a cardiologist in Düsseldorf, became the first person in the world to use patients' own bone marrow cells in the treatment of heart attacks. The experiment was a bold one: the intervention had only been described in mice a few months previously. Other attempts followed, with promising results, but by then experts in the field were becoming highly critical of this overhasty translation into practice. It is now clear that the supposed successes achieved by Strauer's treatment were built on several inconsistencies and practical failings, as British researchers established in several publications. The Heinrich Heine

Photos: MPI for Molecular Biomedicine / Boris Greber; MHH / Mania Ackermann

Berlin-Brandenburg Center for Regenerative Therapies

BCRT

Berlin-Brandenburger Centrum für Regenerative Therapien **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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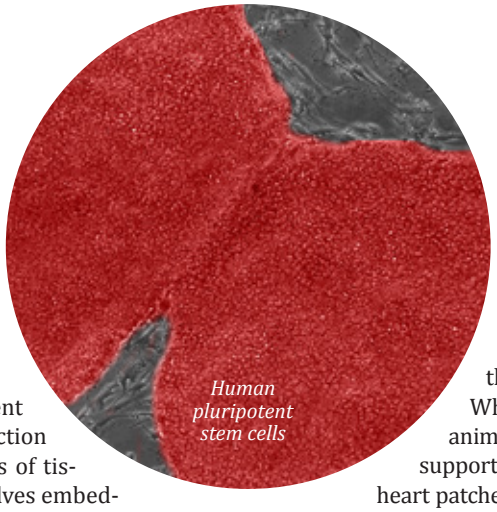
University in Düsseldorf and its university hospital have commenced disciplinary proceedings on suspicion of scientific misconduct.

In the first decade of the 21st century, doctors worldwide began to use various types of cells from bone marrow, either injecting them into the damaged parts of the heart or infusing them into the heart via the coronary arteries. A milestone in cardiac cell therapy was the large-scale REPAIR-AMI study, which involved 204 patients and was led by Andreas Zeiher and Stefanie Dimmeler of Goethe University Frankfurt. The researchers examined the results of stem cell treatment in heart attack patients, using rigorous scientific criteria. They isolated blood mononuclear cells (BMC) from the bone marrow of heart attack patients and then re-administered them. In the double-blind, placebo-controlled and randomized trial, the cell therapy was found to be safe and effective.

However, the beneficial effects for patients were minor. The pumping efficiency of the heart improved on average by two to three percentage points; in the case of extensive infarction the effect was significantly greater. In relation to the combined hard endpoints of death, repeated myocardial infarction, or readmission to hospital, the results are also highly significant statistically. The Frankfurt-based researchers plan to collect more data to substantiate the usefulness of this regenerative therapy. Andreas Zeiher and Birgit Aßmus, together with many other German clinicians, are heavily involved in the major European approval-related Phase III trial known as BAMI, in which patients who have suffered acute myocardial infarction are treated with autologous BMCs using coronary intervention techniques. Experts regard the BAMI trial, which is being funded by the EU to the tune of six million Euros, as pointing the way forward for cardiac stem cell therapy. "In 2019 we shall be able to say whether patients actually have longer and better-quality lives with this treatment," said Zeiher in interview with the GSCN.

Heart muscle cells are the perfect cell type

Researchers do not yet fully understand how the administered bone marrow stem cells actually work in the heart. They have moved away from the original idea that they transform into heart muscle cells inside the heart. "The cells obviously work indirectly via paracrine effects – in other words, they release factors and modulate inflammation processes. But a few days after the injection the cells have disappeared," says Wolfram Zimmermann of the Institute of Pharmacology at University Medical Center Göttingen. The cardiologist believes that the starting material for cardiac cell therapy needs to be extremely well defined in order to make trial results more comparable.


Human pluripotent stem cells

For substantial regeneration of infarcted hearts, Zimmermann relies on cells of another type – heart muscle cells. "If you want to replace lost and scarred heart muscle tissue, cardiomyocytes are the only option," says Zimmermann.

His Göttingen-based team has spent many years working on the production of heart-tissue constructs by means of tissue engineering. Their method involves embedding large numbers of heart muscle cells in a collagen matrix. The resulting patches have been christened "engineered heart muscle." The 16 cm2 tissue patches each contain around 40 million cardiomyocytes. "In recent years we have optimized the engineering process so that it operates robustly and under GMP conditions and can be transferred to clinical practice," says Zimmermann.

Cells travel across the Atlantic

To produce the heart muscle cells in large quantities, the researchers use human ES and iPS cells. These cells are produced in the US – in the laboratory of Larry Couture at City of Hope, using a technique developed by Joseph Wu of Stanford University. It is a German-Californian cooperation project supported by the Federal Ministry for Education and Research (BMBF) and the California Institute for Regenerative Medicine (CIRM). The cardiomyocytes are shipped to Germany, where the researchers in Göttingen use them to make the tissue constructs. Some of the heart muscle patches are even sent back to California. For Zimmermann this demonstrates how transatlantic cooperation can work: "We can overcome the logistical challenges: the shipped cells survive the journey without problems," he says.

He sees the future of cell therapy as being "allogeneic," with preparations based on cell material that is not taken from the patient: "Everything else is impractical and prohibitively expensive, especially when a broad medical application such as myocardial infarction therapy is involved." The researchers have already obtained impressive results by using their tissue constructs in rats and mice: when implanted in coronary scar tissue, the cell patches integrated well, the cells actively contracted and even integrated electrically, so that pumping performance increased. When human cell patches are used in animals, the transplants still survive and support the functioning of the heart. The heart patches will be tested next in experiments on large animals. "If the treatment is found to be safe, we want to start a clinical trial in Göttingen and Stanford in a couple of years. It would be the first clinical trial of artificial heart tissue in humans – with all the challenges that brings," says Zimmermann.

Heart patches also being tested in Hannover

The team led by Ulrich Martin is pursuing a similar goal at the REBIRTH Cluster of Excellence at Hannover Medical School. "We want to inject heart muscle cells derived from iPS cells into infarcted hearts or administer them via tissue patches," says Martin, who is also currently President of the GSCN. Following successful tests in rodents, his team has also started experiments on large animals as a means of testing the cell replacement therapy. They are aiming to conduct the first clinical trial in five years. Martin considers the risk of the transplanted cells degenerating in the body and forming tumors to be small. "The technologies are now sufficiently safe and reliable for us to be able to produce good-quality cells in large quantities." But he comments that a suitable blood-vessel supply for thicker cell patches is still needed. This is something that the regenerative medicine experts in Hannover are currently working on.

These examples of the use of stem cells in cardiac therapy show that the latest generation of cell therapies could find their way into German hospitals in the not-too-distant future.

Text: Philipp Graf

Photo: MHH / Mania Ackermann

Center for Regenerative Therapies Dresden (CRTD)

DFG Research Center and Cluster of Excellence at the TU Dresden

At the DFG Research Center for Regenerative Therapies Dresden (CRTD), Cluster of Excellence at the TU Dresden scientists are seeking to understand the mechanisms of regeneration using model organisms to translate the results to man and to develop novel regenerative therapies for thus far incurable diseases. The center's major research areas are focused on hematology/ immunology, diabetes, neurodegenerative diseases, bone regeneration and technology development.

Currently, eight professors and nine group leaders are working at the CRTD. They are integrated into a network of over 80 member labs at 7 different institutions in Dresden. In addition, 21 partners from industry are supporting the research projects. The synergies in the network allow for a fast translation of results from basic research to clinical applications.

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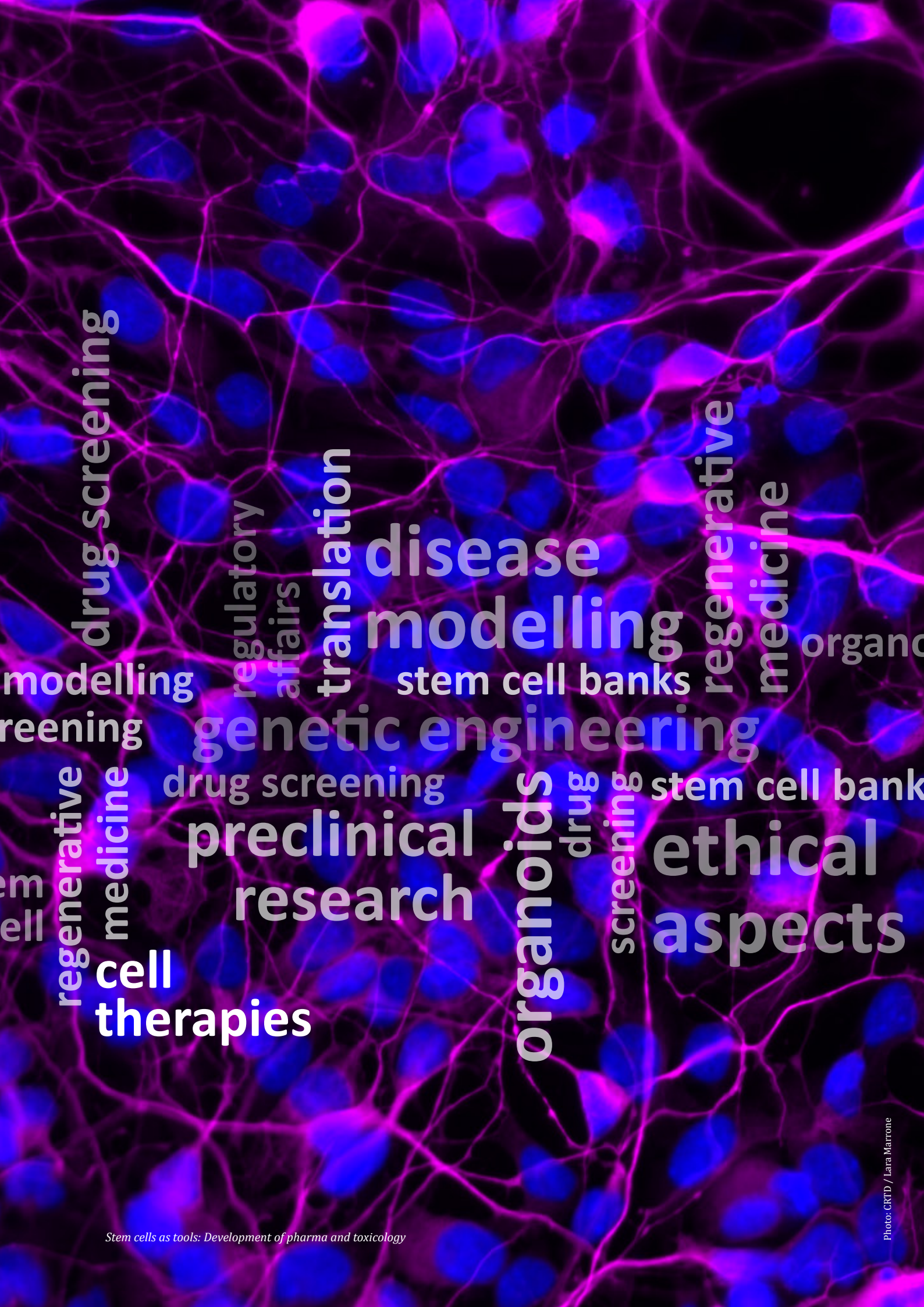

Stem cells as tools: Development of pharma and toxicology

Photo: CRTD / Lara Marrone

Interview with Egbert Flory on the authorization of cell therapies

"Stem cells need flexible rules"

Anyone seeking to manufacture stem cell-based medicinal products are obliged to fulfil the authorities' regulatory requirements when moving into clinical application. It is important to retain an understanding of this situation. If stem cells undergo additional engineering on their way to becoming a finished product, they are classified as Advanced Therapy Medicinal Products (ATMP) within the EU. They will then require a centralized marketing authorization from the European Medicines Agency (EMA).

Egbert Flory, a virologist at the Paul Ehrlich Institute (PEI) in Langen, is one of Germany's leading experts in ATMP regulations. He made major contributions to preparing the EU regulation that came into force at the end of 2008, and continues to serve on the EMA committee responsible for decision-making on ATMPs. At PEI, Flory is the deputy head of the Medical Biotechnology Division. In addition to managing the regulatory work there, he also runs his own laboratory that performs research into stem cells.

Mr. Flory, what are the current major developments in the field of stem cell-based medicinal products in Europe and in Germany?
Ever since the ATMP regulation entered into force in 2008, we have been experiencing a sharp rise in clinical developments and applications for stem cell therapies – particularly those that are based on adult stem cells, such as mesenchymal stem cells (MSCs). Surveys show that just below 200 European clinical studies are focusing on stem cells. I'd estimate that Germany has about 35 such studies. So far, there are no clinical trials or approved ATMPs based on iPS cells in Europe. However, developers have been seeking out scientific advice for this area – including in Germany. Several EU member states currently also host a number of clinical studies that are using human embryonic stem cells as their starting materials.

Why are stem cell-based products such a big challenge from a regulatory point of view?
Stem cells are extremely diverse, so it is difficult to characterize them. Furthermore, the different types of cells have very different risk profiles. This presents major challenges for regulators and the applicants themselves. Even the starting material is highly heterogeneous: there are pluripotent stem cells, adult stem cells, and a variety of "precursor cells." The manufacturing processes are usually very complex, and biological assays are often not established and validated in a pharmaceutical sense. In some cases, only a few relevant animal models are available for the non-clinical development phase. Besides, the individual characteristics of patients also makes things complicated.


Egbert Flory

Photo: PEI / Egbert Flory

In your view, what functions should a regulatory framework for stem cell-based therapies fulfill?
As is the case with conventional medicinal products, it is primarily a question of quality, safety, and efficacy. However, for years my mantra has been that we desperately need a flexible regulatory framework for stem cell-based medicinal products. They have to be considered individually, on a case-by-case basis. To achieve this, we need a close, multidisciplinary collaboration between scientists, expert organizations, and regulators. Regulatory decisions regarding stem cell products must be based on scientific knowledge and must take into account the specific risk profile of the cells.

The regulatory authorities call stem cell-based products ATMPs. This means they fall within a European legal framework. What are the key points of the EU's ATMP rules?
The EU regulation on ATMPs entered into force in December 2008. This created a harmonized, EU-wide process for the highly complex and innovative cell-based therapies. Essentially, this means that these types of products cannot be placed on the European market without having received approval centralized marketing authorization. The European Medicines Agency is responsible for granting the latter, and reaches its decisions in London. A special EMA committee was also set up – the Committee for Advanced Therapies (CAT) –to take charge of ATMPs as a special group of medicinal products..

What exactly is the CAT's role?
The CAT is the body that reviews all the data on a product. Thus, for ATMPs in Europe, it is the supreme committee for preparing a decision on an authorization via

providing developers with scientific advice, and providing expertise during inspections. The state authorities carry out the pharmaceutical monitoring, including the inspections. They also grant the manufacturing authorizations for ATMPs, based on the European Good Manufacturing Practice guidelines. The state authorities also categorize medicines in accordance with pharmaceutical legislation – they perform the classification, which is legally binding in Germany.

Have there been any notable changes to the ATMP rules in recent years?

The regulations are based on the EMA's Guideline on Human Cell-based Medicinal Products from 2007. This is the parent guideline for all cell-based therapies, and it was a global pioneer. Even back then, the aim was to remain open and flexible. In 2010, the CAT published the world's first stem cell guideline, which also has a great deal of influence outside Europe. In recent years, the CAT has also focused extensively on the classification of cell-based medicinal products. Stem cell-based products are not only considered as ATMPs when they have been "substantially manipulated" using biotechnological processes; cell products are also classified as ATMPs if they are applied in a "non-homologous" manner – in other words, if the cells have different functions in the donor and the recipient. The CAT published classification recommendations relating to these aspects last year. The observations contained in this "reflection paper" are especially helpful with regard to stem cell products.

the European Commission. Every member state appoints two experts to the committee. My PEI colleague Dr Martina Schüssler-Lenz and I are currently the members for Germany. The CAT makes the decisions, provides scientific advice, and assigns the cell products according to their properties, i.e. performs the so-called classifications. The committee considers future developments in the ATMP field. We meet at least once a month. The CAT also includes members who represent patients and clinicians. This diversity is rare at the EMA and underscores the committee's very multidisciplinary approach.

What are the tasks of the Paul Ehrlich Institute (PEI) and the state authorities here in Germany?

As a federal authority and national licensing authority for biomedicines, the PEI is legally responsible for all processes relevant to ATMPs – i.e. for authorizing clinical studies,

How many ATMPs have been approved in the EU to date?

Six products have been approved in the EU so far, and the process is underway for four others.

That is rather a low output.

Photo: MDC

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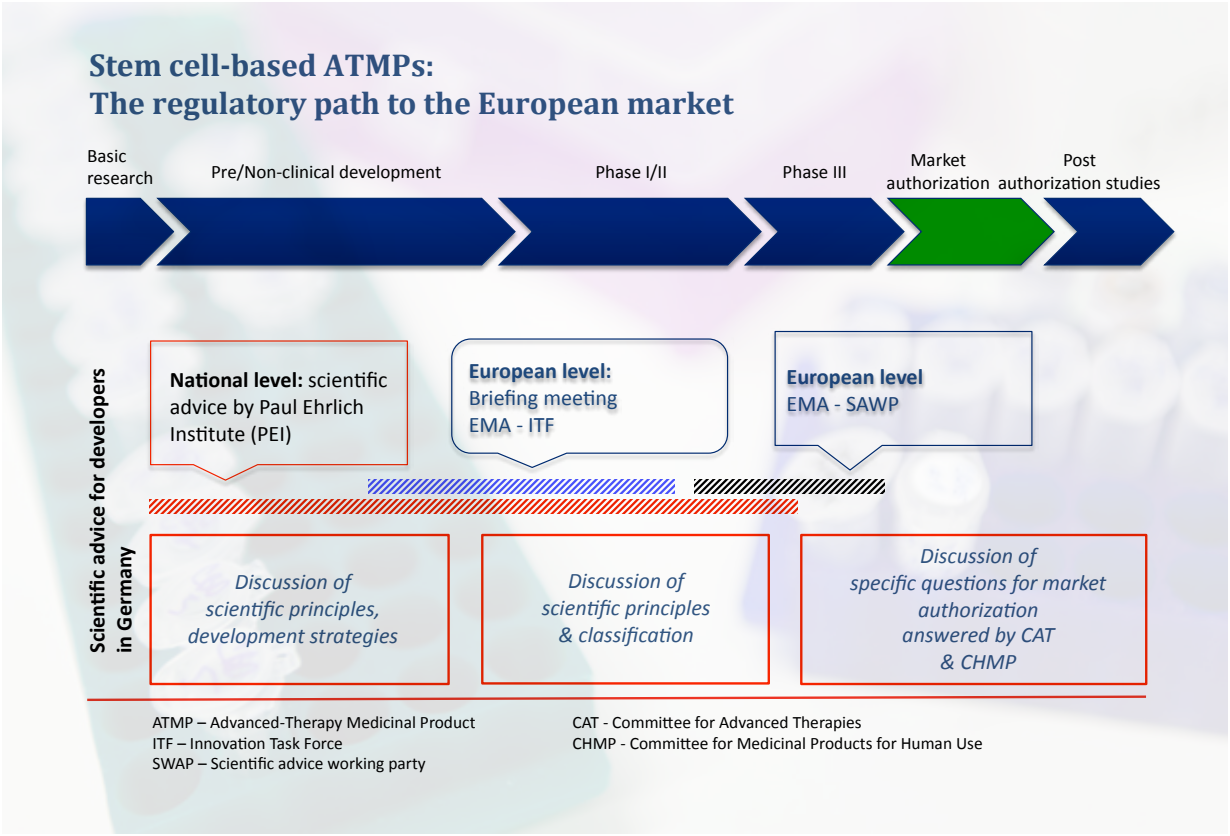

I don't see it that way. The number is appropriate for a field that is still in its infancy. It is important to remember that we are dealing with very complex, innovative, and scientifically oriented products. Not so many of those exist. And the number of applications is rising steadily. Authorizations in this field are just as rare in the U.S. and Japan as they are here in Europe.

There was of course an important premiere in April 2015, when Holoclar became the first stem cell therapy to be granted a marketing authorization in the EU. How does this product work?

Holoclar is a stem cell treatment used in the eye. It is intended for patients who have suffered damage to the surface of the cornea, for instance as a result of physical or chemical burns. Limbal stem cells are removed from the edge of the patient's cornea, cultivated in the laboratory, and then re-transplanted into the damaged areas. An Italian company manufactures the product. The clinical data were convincing, with many patients experiencing improvements to their eyesight. The product was granted what is known as a conditional authorization. This means that additional confirmatory clinical studies are being run in several centers, including in Germany. The developers thus have to submit further data on the efficacy of the medicinal product.

What went well with Holoclar? What can future developers learn from it?

It was the fastest ATMP process that my team and I have handled so far. Once the application had been submitted, it took just one year to reach a decision. The manufacturer in Italy was very well connected and organized. Another plus point was that the scientific development work, which had lasted many years, was extremely good and transparent. Overall, that is the ideal basis for our regulatory work. It means we can still work if there are only limited data from non-clinical studies or if no randomized clinical trials have

Photo: MDC / Graphic: PEI / Egbert Flory

been carried out. We are gaining many valuable experiences from the first approved stem cell product. This will certainly facilitate the process for subsequent applicants.

When it comes to developing a stem cell-based medicinal product, how important is the classification?
Classification first involves defining which medicinal track companies or universities are involved in their product. I think it is important that developers know this at an early stage. Seeking a recommendation for a classification is often the first contact that an applicant has with the relevant authority. However, an EMA classification – which takes about six weeks – is not a legally binding scientific recommendation. In Germany, the state authorities are responsible for legally classifying medicinal products. It is not an official task of the PEI, but since we obviously have specialist expertise in the field, the state authorities generally ask us for advice.

At the Paul Ehrlich Institute, you offer scientific advice to medicinal product developers. How does this work?
Since 2009, the PEI Innovation Office has been providing interested parties with advice on ATMP development at any time. Fortunately, many developers have shed their initial hesitance to make contact. We conduct about 50 advisory sessions a year. These might be intensive consultations similar to those held at the EMA, or they could be orientation discussions, which involve an informal chat without any major documentation. Seeking advice makes particular sense in the early phase of product development and in the run-up to clinical studies, as it can help developers avoid potential errors that will require a lot of extra work and money at a later stage. The costs are also attractive: the hourly rate per expert is just € 68.

After a marketing authorization has been granted, companies have to start grappling with the problem of cost reimbursement at a national level.
Unlike the authorizations, cost reimbursement is not organized centrally in Europe. Each country therefore decides how the costs of a therapy are to be reimbursed and who is responsible for it. We have comparatively generous reimbursements for cell-based therapies here in Germany. The situation is very different in other EU countries. That can be frustrating for manufacturers. Take, for instance, Provenge, a tumor vaccine for prostate cancer that was authorized as an ATMP in 2013. The manufacturers of this immunotherapy have since withdrawn the EU marketing authorization because the future reimbursement situation in Europe was unresolved. Germany was the only EU country where health insurance providers reimbursed the costs. The EMA and PEI are now working very hard to include reimbursers in the scientific advisory sessions at an early stage – i.e. before the authorization process begins.

What does the term "hospital exemption" mean? How does the rule affect developers of stem cell-based therapies in Germany?
The exemption, which is anchored in the ATMP regulation, exists because a great deal of innovation happens in hospitals, and because local production and application are very common. The European Commission formulated the exemption in order to allow these non-routine applications to be used in hospitals in a very limited way. EU countries have taken quite different approaches to implementing it. Germany has implemented it in a very interesting manner, I think: once innovative products receive PEI authorization, hospitals can use them on patients to a limited extent. The manufacturing and processing can be done by a toll manufacturer.

Photo: MDC

The Collaborative Research Center SFB 873

Maintenance and Differentiation of Stem Cells

The Collaborative Research Center SFB 873 "Maintenance and Differentiation of Stem Cells in Development and Disease" at Heidelberg University works towards defining the regulatory principles underlying the balance between maintenance, expansion and differentiation of stem cells in diverse systems on a mechanistic level. To this end the SFB873 studies a wide spectrum of experimental models ranging from plants to human to elucidate the inherent properties of specific stem cell systems, but also to uncover common and divergent principles behind regulatory regimes and molecular signatures.

Our consortium brings together internationally recognized researchers, with unique scientific strengths in cell biology, biophysics, developmental biology, molecular medicine or modeling. With our research we hope to advance our understanding of principles underlying stem cell function and lay the foundation for translational approaches.

Centre for Organismal Studies (COS)
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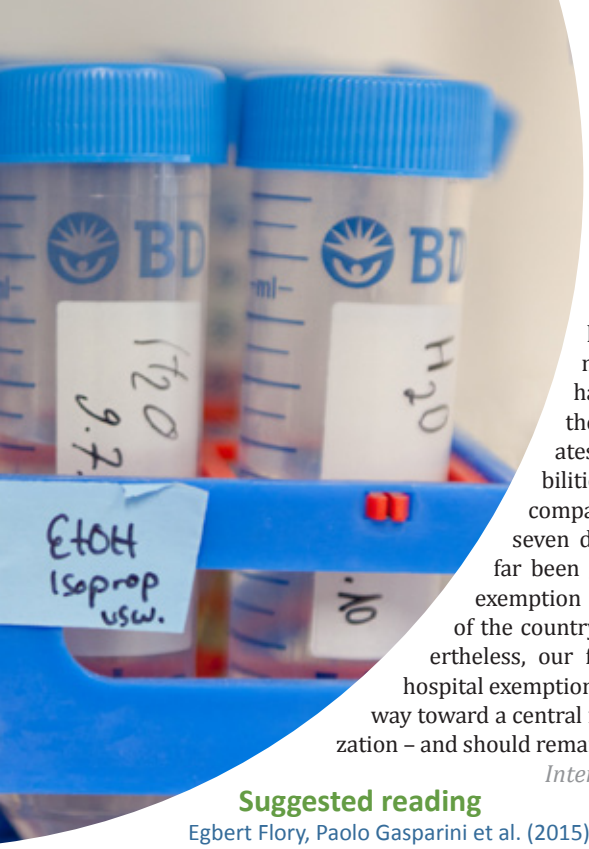


The manufacturer has to be in Germany but does not have to be located in the hospital. This creates interesting possibilities for specialized companies. In Germany, seven developers have so far been granted a national exemption under Section 4b of the country's Drug Law. Nevertheless, our feeling is that the hospital exemption is a step along the way toward a central marketing authorization – and should remain an exception.

Interview: Philipp Graf

Suggested reading

Egbert Flory, Paolo Gasparini et al. (2015), "Regulatory viewpoints on the development of advanced stem cell–based medicinal products in light of the first EU-approved stem cell product", **Cell & Gene Therapy Insights**, ***DOI:10.18609.cgti.2015.010***

What are ATMPs?

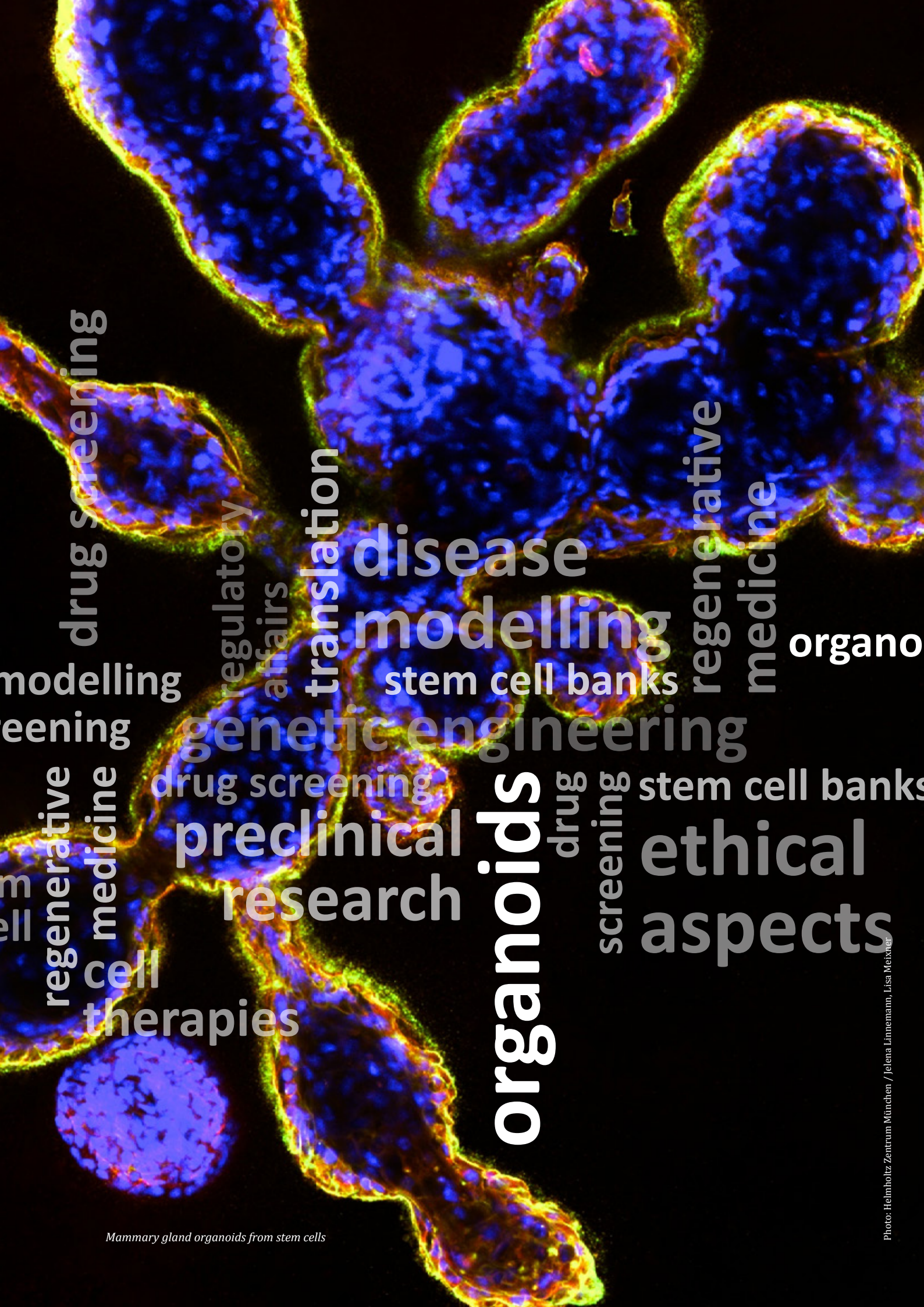
Cell-based medicinal products that contain living or non-living cells and were engineered during manufacturing are legally classified as Advanced Therapy Medicinal Products (ATMP) in the EU. The European Medicines Agency (EMA) is responsible for the marketing authorization of these products. ATMPs are divided into different classes: gene-therapy medicines, tissue-engineered products, somatic-cell-therapy medicines, and combinations thereof. Six products have been granted a marketing authorization in the EU since the ATMP regulation entered into force:

Product name	Manufacturer	Year of EU marketing authorization
ChondroCelect	TiGenix	2009
Glybera	UniQure	2012
Provenge	Dendreon	2013 [1]
MACI	Genzyme	2013 [2]
Holoclar	Holostem Advanced Therapies	2015
Imlygic	Amgen	2016

[1] Since withdrawn at manufacturer's request

[2] Suspended due to manufacturing stoppage

Disclaimer: Please take notice, that the online version of the interview is slightly different to the printed version due to further editing.



Mammary gland organoids from stem cells

Photo: Helmholtz Zentrum München / Jelena Linnemann, Lisa Meixner

Stem cell-based disease models

Organoids: 3D miniatures are booming

"Organoids" are as tiny as mustard seeds, but many biomedical scientists believe they are the next big trend in health research. Using sophisticated 3D tissue culture techniques, researchers are becoming increasingly skilled at combining stem cells and differentiated cells to create miniature versions of organs such as brains, intestines, and stomachs. The topic is also attracting more and more stem cell researchers in Germany. Organoids are so similar to the full-sized organs on which they are modeled that they have opened up new avenues for investigating principles of developmental biology and disease etiologies. This means that the mini-organs are not only good candidates for testing active substances, they also have enormous potential for diagnostics and regenerative therapies.

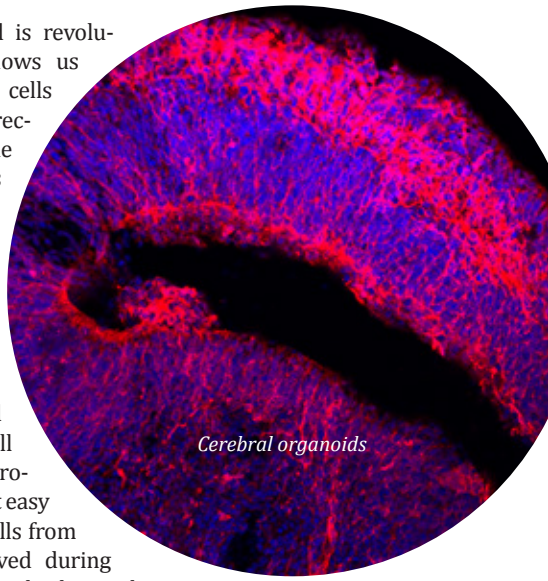
Sina Bartfeld is delighted every time she looks at her mini-stomachs, just days old, through the microscope: "My organoids are so beautiful," says Bartfeld, a biologist who is currently setting up her own group at the University of Würzburg. The delicate, hollow spheres are made of a single layer of cells and measure just under half a millimeter. Smaller bubbles are budding around their edges. "As well as various differentiated cell types, these also contain the stem cells that constantly replenish the stock of cells," says Bartfeld. It takes less than two weeks for a tiny stomach to grow. "The fascinating thing is that the stomach organoids self-organize and keep growing," says Bartfeld.

Bartfeld is one of a rapidly increasing number of scientists whose work with organoids is changing biomedical research. From miniscule intestines and lungs to diminutive mammary glands and brains, tiny versions of almost every organ in the human body are flourishing in laboratories all over the world. As well as resembling the full-sized organs in appearance, the in vitro organoids also carry out astoundingly realistic complex biological processes.

Bartfeld moved to Würzburg from Utrecht in the Netherlands last fall. As a postdoc, she worked at the Hubrecht Institute for Developmental Biology, in the working group of Hans Clevers, a Dutch stem cell researcher who is considered the pioneer and initiator of the recent cell-culture boom. From the elite training center of the Hubrecht Institute, organoid technology is now conquering research laboratories all over the world.

Adult stem cells back in the spotlight

Three-dimensional cell cultures are not a new trend. Researchers involved in the differentiation of pluripotent stem cells are familiar with "embryoid bodies," three-dimensional clumps in which the cells develop much faster than they would in the body. Tissue engineers have also spent many years experimenting with 3D aggregates made from different types of cells.



Cerebral organoids

"Hans Clevers' method is revolutionary because it allows us to isolate adult stem cells from organs and to recreate their niche in the Petri dish," explains Bartfeld. Clevers and Toshiro Sato first accomplished the feat in 2009, with tissue from the small intestine. One of the keys to the team's success was that they had identified an important stem cell surface marker (the protein LGR-5) that made it easy to isolate adult stem cells from intestinal tissue removed during surgery. The marker can also be used to find adult stem cells in other tissues. Sophisticated cell-culture techniques paved the way for another step forward: by adding Matrigel, a gel-like secretion from mouse tumor cells, the scientists made a very good version of the immediate environment ("niche") of adult stem cells. Once they are embedded in this extracellular matrix, the cells find themselves in very comfortable surroundings. Adding growth factors and a few other types of cells was then enough to make the adult stem cells do in the Petri dish what they would do in an actual intestinal wall: renew themselves while simultaneously producing structures like villi and crypts. As a result, a self-organizing, living intestinal system grew in the Petri dish.

Realistic model systems for diseases

"This culture technique provides an inexhaustible source of human cells from a specific type of tissue," says Bartfeld. "And what is more, the cells are unchanged." Bartfeld explains that this means the organoids get much closer to the natural, in vivo situation than cell aggregates, which are obtained using pluripotent stem cells. Another advantage is that it is easy to learn how to obtain the cells and perform the culture technique. The mini-organs are also easy to handle. "Freezing, defrosting, mailing – none of that is a problem," says Bartfeld. Bartfeld explains that the field exploded after Nature published the discoveries in 2009. Adult stem cells, which had retreated into the background in the era of iPS cells, returned to the spotlight. From then on, many of Bartfeld's colleagues in Utrecht began picking out their own organ system.

As cell-based model systems, organoids are not only well suited to studying organogenesis and the developmental biology of tissues. They also open up entirely new scope for investigating disease mechanisms. At the Institute for Molecular Infection Biology in Würzburg, Bartfeld is hoping to

Photo: Helmholtz Zentrum München / Marisa Karow

use her mini-stomachs to recreate the development of peptic ulcers. To do so, she is infecting the 3D structures with Helicobacter pylori bacteria and observing closely how the germs cause cancer to develop. "This means we can simulate and examine in more detail the interaction between the pathogen and the human host cells." Bartfeld's initial experiments have already shown that in organoids infected with the stomach bacteria, key steps involved in the innate immune response occur correctly, although the pattern varies depending on the type of cell.

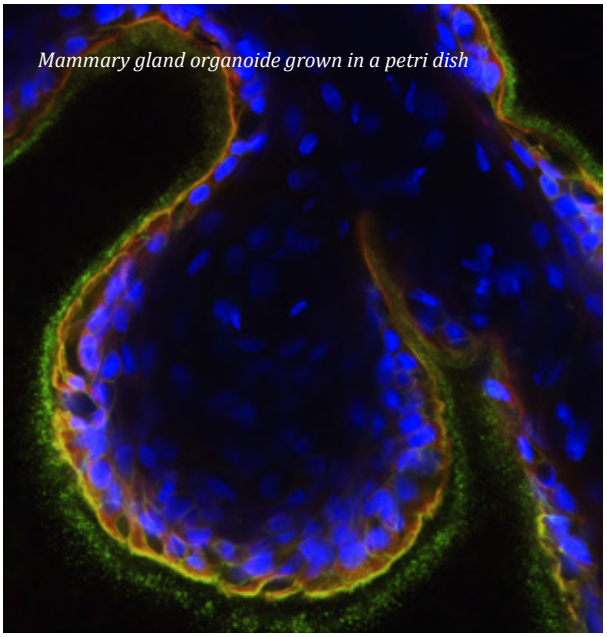
Another potential application is in regenerative medicine. For instance, Bartfeld has succeeded in making mini-stomachs from patients who have had their stomachs removed to treat cancer. "One use for these cancer organoids is to test which medicines are effective and which are not," says Bartfeld. She also explains that the organoids can be used to simultaneously cultivate and compare healthy and diseased tissue from the same patient.

Henner Farin, who since September 2015 has been running a young researchers' group at the Georg Speyer Haus in Frankfurt as part of the German Consortium for Translational Cancer Research (DKTK), is another protégé to come out of Clevers' laboratory and return to Germany. Farin plans to produce intestinal tumor organoids and use them to research the mechanisms of carcinogenesis. He is also planning to use patient-specific organoids to investigate chronic inflammatory intestinal diseases.

News from the organoid workshops

Another reason why health researchers are attracted to working with organoids is that they are easy to combine with other cell technologies. For instance, scientists can equip them with cell types derived from induced pluripotent stem cells (iPS cells). Individual cells in the miniature organs can also be modified or reprogramed using genome editing. This means the 3D structures can be tailored for a specific disease model.

The GSCN annual conference in September 2015 showcased what researchers working on 3D cell cultures are now capable of. Hans-Willem Snoeck of Columbia University in New York reported on his attempts to recreate the development of a human lung as naturally as possible in the Petri dish. With the help of iPS cells and a sophisticated protocol, his team has made remarkable progress. "We have succeeded for the first time in allowing the fine branching and the maturation of the alveoli to occur in the Petri dish," says Snoeck. In addition to producing insights into developmental biology, the models can also be used to study numerous lung diseases, such as the flu, cystic fibrosis, and lung cancer.



Mammary gland organoide grown in a petri dish

Photo: Helmholtz Zentrum München / Jelena Linnemann, Lisa Meixner

A team led by Christina Scheel at Helmholtz Zentrum München, meanwhile, has succeeded in recreating the complex 3D structures of the mammary glands. The Munich researchers isolated stem cell-like cells from tissue removed during cosmetic breast-reduction surgery. In the 3D culture, the cells begin forming complex milk ducts that end in bubble-like structures. The researchers now want to use the mini-breasts to examine the development of breast cancer in more detail.

Reprograming mini-brains

No organoid has caused as much of a stir over recent years as the pea-sized mini-brains that have been grown in Jürgen Knoblich's laboratory at the Institute of Molecular Biotechnology in Vienna. Neural precursor cells derived from iPS cells began, almost of their own accord, combining to form so-called cerebral organoids. The little balls of neural tissue resemble, both outwardly and in terms of their molecular biology, the structures of a young embryonic brain.

"In 2013, this work was definitely an eye-opener for the field and created a great sense of optimism," says Benedikt Berninger of the Institute for Physiological Chemistry at the University of Mainz. His working group is one of many in Germany that have begun focusing on cerebral organoids. "We use the mini-brains as a platform for studying the reprograming of glial cells to form neurons," explains Berninger. His colleague Marisa Karow carries out cell transplants on the tiny brains – a kind of open brain surgery in the Petri dish. It is then possible to follow the consequences of this intervention in real time. The mini-brains have also given the neuroscientists new avenues for deciphering the molecular programs that occur in developmental disorders in the brain.

Berninger believes that the current wave of euphoria surrounding the organoids is absolutely justified, but adds that "we are still in the early phases." He says that the research is expensive and complex, and that key questions relating to the long-term survival of the cell cultures have yet to be answered. The cell-culture experts are still trying to work out how best to look after and feed the organoids over a period of many months. Berninger is campaigning for better networking of the knowledge and expertise within the growing research community in Germany. Julia Ladewig in Bonn, Frank Edenhofer in Würzburg, and Magdalena Götz in Munich are just some of the stem cell researchers whose teams are working intensively on the living 3D brain models.

"We, too, are enthusiastically following and participating in the progress being made with organoids," says Hans Schöler, Director of the Max Planck Institute for Molecular Biomedicine in Münster. The Max Planck researchers are using brain organoids as test objects for the targeted reprograming of astrocytes to form precursor cells. "We hope that this will improve our understanding of neurodegenerative ageing processes," says Schöler. "Right now, organoids are a vast playground."

Text: Philipp Graf

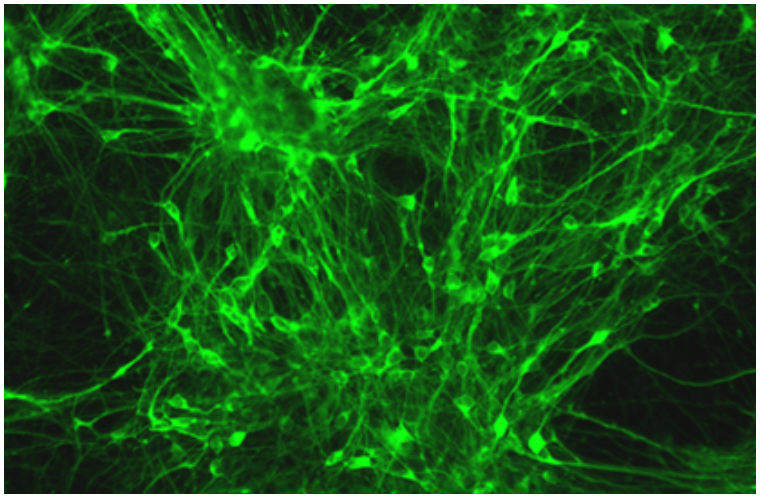
New kits on the block…

ThermoFisher SCIENTIFIC

„Pure, what do you mean, pure?!?!?" Albert grumbled. "It's not so easy to make pure Dopaminergic Neurons for Parkinson's disease research. I always see a certain degree of "contamination" with fore- and hindbrain Dopaminergic Neurons during differentiation from iPSCs and ESCs. For example, I just recently used a kit, which was easy to use and gave me high yields of NSCs from my iPSCs. However when further differentiating these NSCs, I achieved not only midbrain DA Neurons, which Parkinson's researchers are mostly interested in, but I also noticed the presence of a significant number of fore- and hindbrain DA neurons. In this case, the ease-of-use advantage actually turned out to be a disadvantage for this specific application."

"Well, darling, that is interesting to hear, but how can I be of help in this case?" asked Josephine, the lovely wife of Albert, who didn't have a clue about research.

"Dad" said Madeline their daughter, a Ph.D. student in her second year, as she joined the discussion, "I just heard about a new kit, which might fit perfectly with your work. With this new kit you can differentiate midbrain dopaminergic neurons from iPSCs and ESCs. That is what your Parkinson's researchers are looking for, right? I even saw some data on the new kit, which provides a simple to use and reproducible protocol, and is even quicker to use than most of the protocols in common use today. You only need 38 days to get to generate your desired mid-brain dopaminergic cell type, which is 7 days shorter than the 45 days required by most protocols. But much more importantly", said Madeleine as she started to become euphoric, "you can make a break in between! Yes, you can efficiently expand and bank your progenitor cells! This allows you to start your differentiations from an intermediate stage next time around using the same batch cells and avoids you having to go all the way back to the iPSC or ESC stage!"

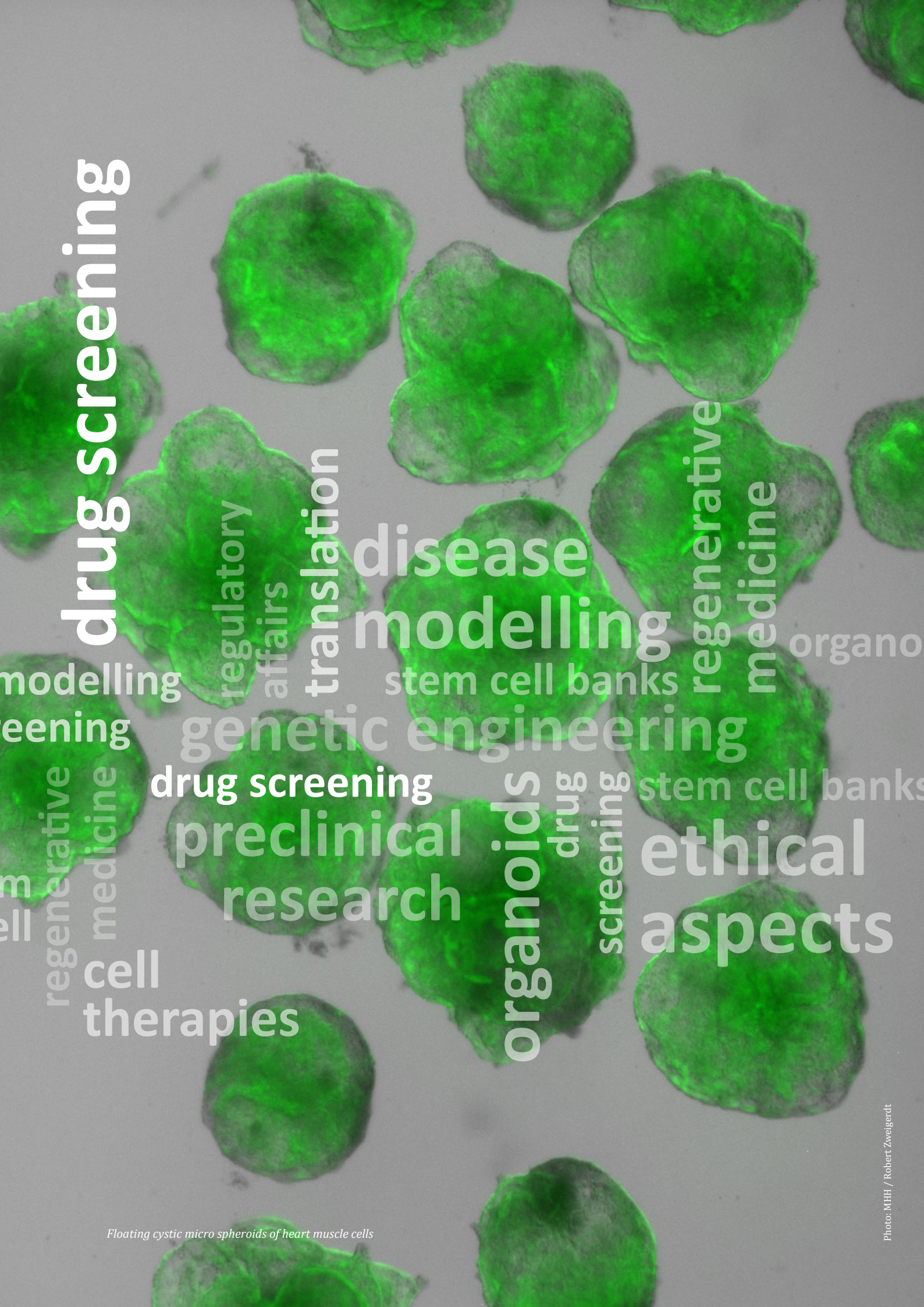


"Wow, that sounds interesting!" said Alfred, interrupting Madeleine, "Thanks for the tip! Do you recall which company makes this kit?"

"That's the new kit from Thermo Fisher Scientific and it is called PSC Dopaminergic Neuron Differentiation kit or something like that. Just yesterday I received the link from one of my lab mates:

www.thermofisher.com/de/de/home/life-science/stem-cell-research/stem-cell-differentiation/psc-dopaminergic-neuron-differentiation.html

Just check out the homepage! Oh, sorry, but I have to leave now!" and Madeleine ran off in a hurry as The Big Bang Theory had just started on TV.



Floating cystic micro spheroids of heart muscle cells

Photo: MHH / Robert Zweigerdt

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.

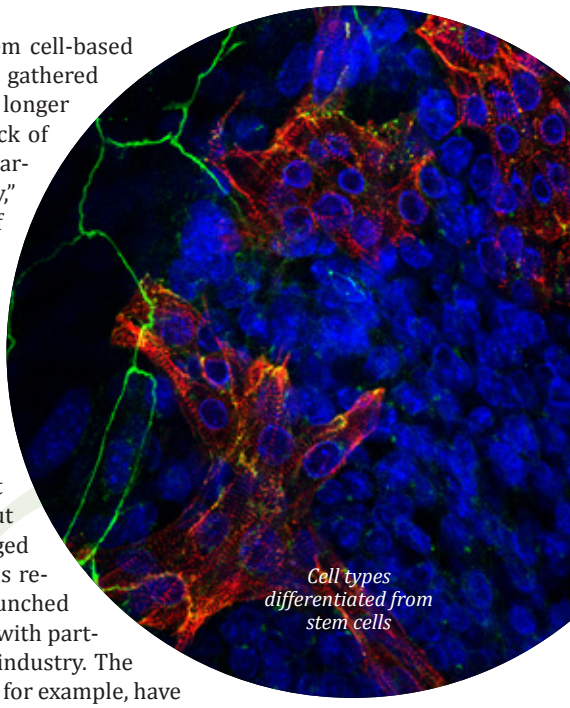
A new era in pharmaceutical research

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.

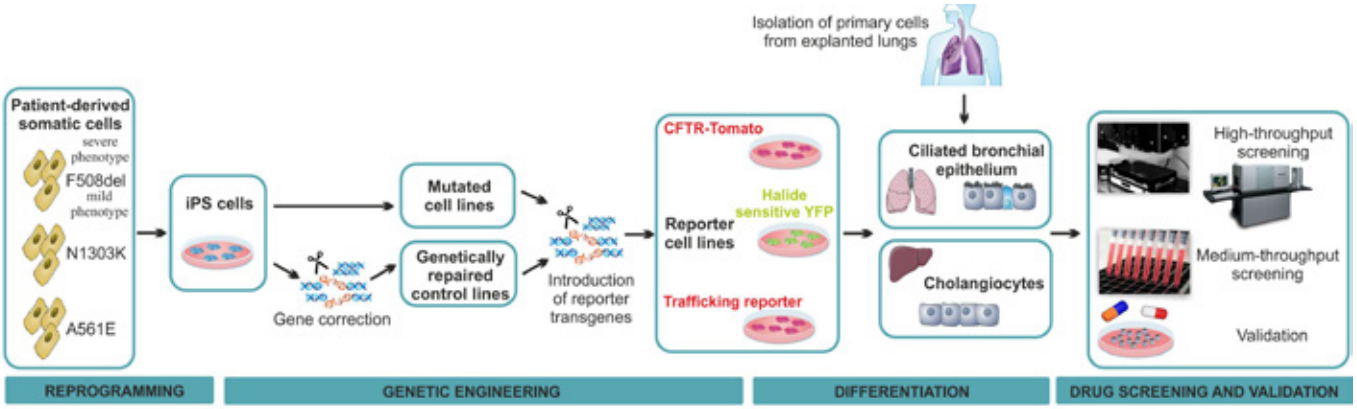
New translation centers set up

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



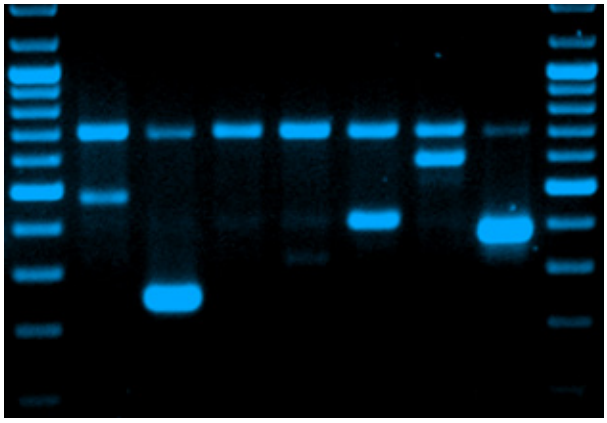
Cell types differentiated from stem cells

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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53105 Bonn
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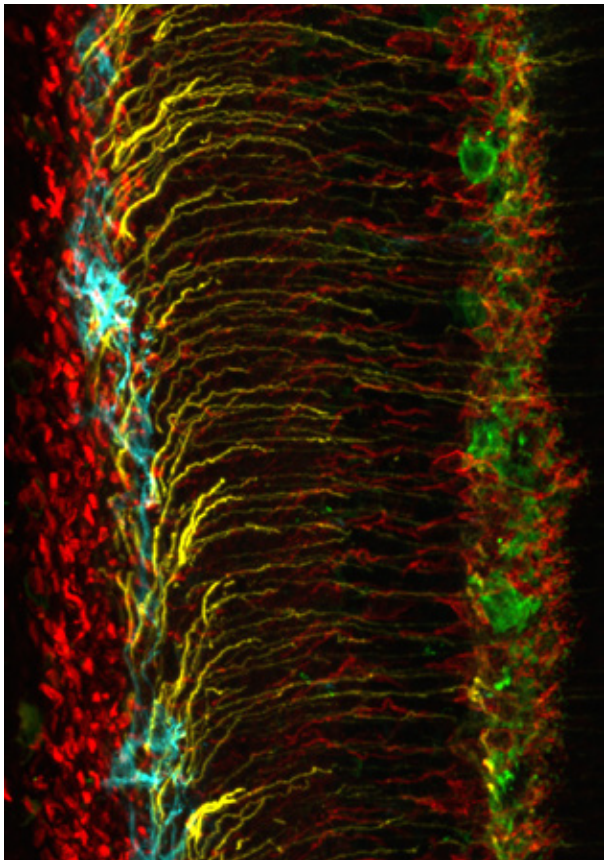
CARE comes to Munich

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

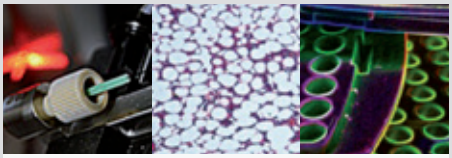
HI-STEM gGmbH is a non-profit public-private partnership between the German Cancer Research Center (DKFZ) and the Dietmar Hopp Foundation (DHS).

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)



HI-STEM gGmbH
German Cancer Research Center (DKFZ)
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69120 Heidelberg
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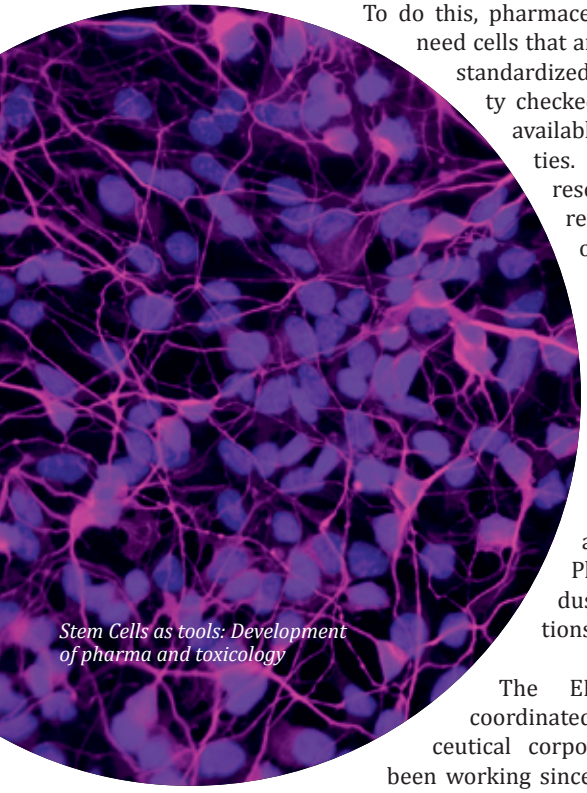
genes we can carry out high-throughput screening of drug libraries." The research partners are a very international group, with representatives from Italy, Portugal, the Netherlands and Canada. Interesting substances will be taken as far as the pre-clinical phase of drug development.

Two IMI consortia on iPS cells

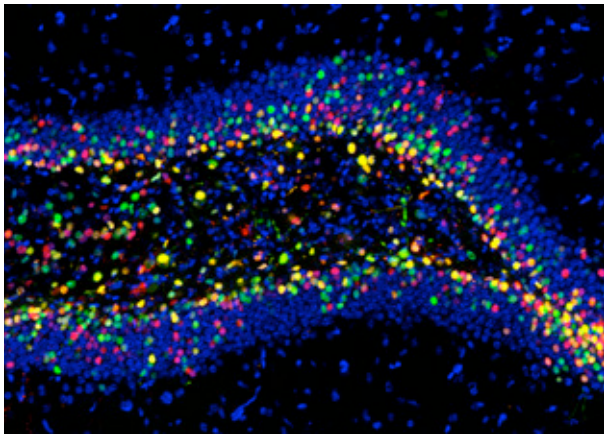
Stem cell-based techniques not only help in the identification of new drugs: In pharmaceutical research, they have also become important tools in the lead validation and optimization of drug candidates found through conventional means.



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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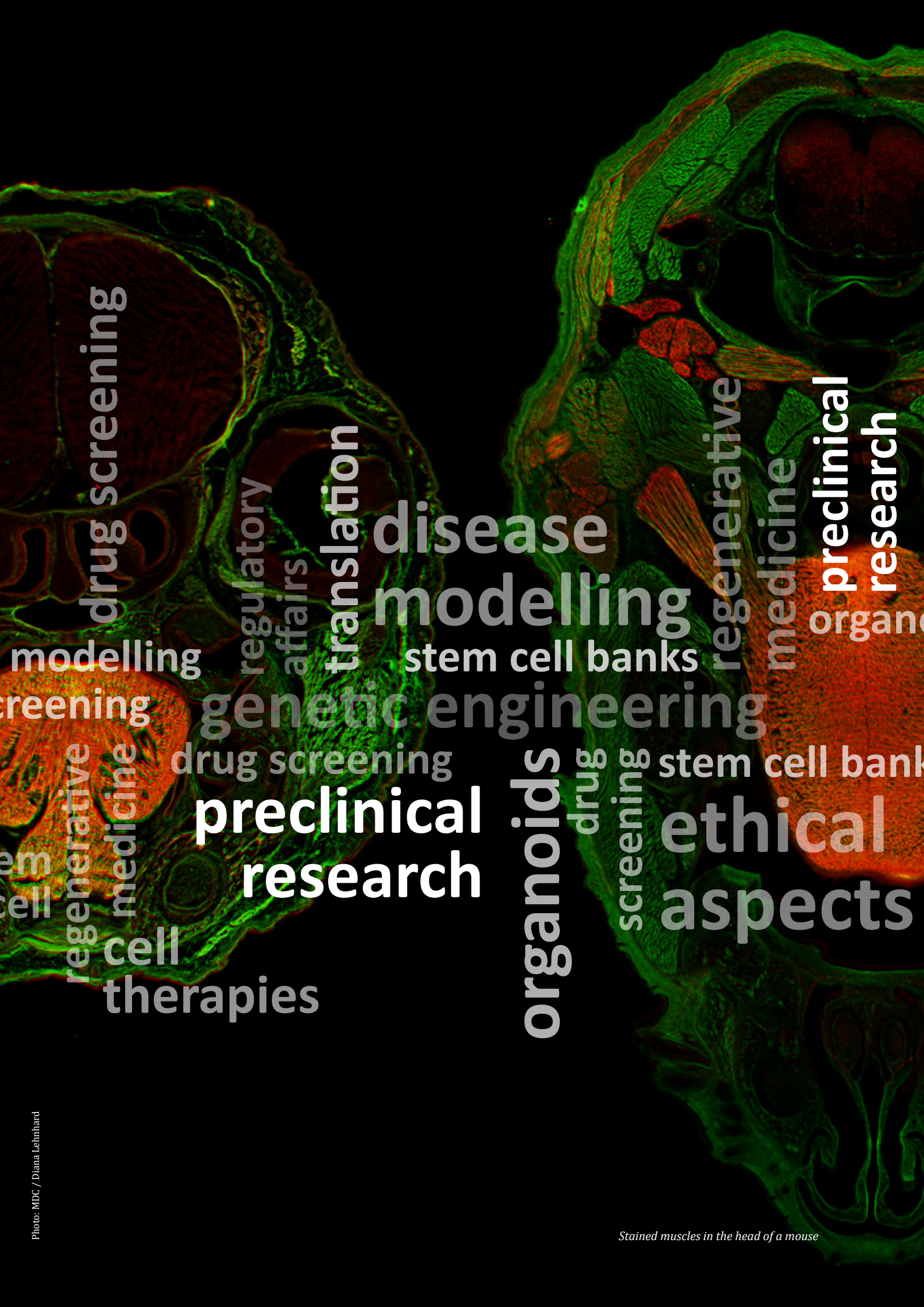


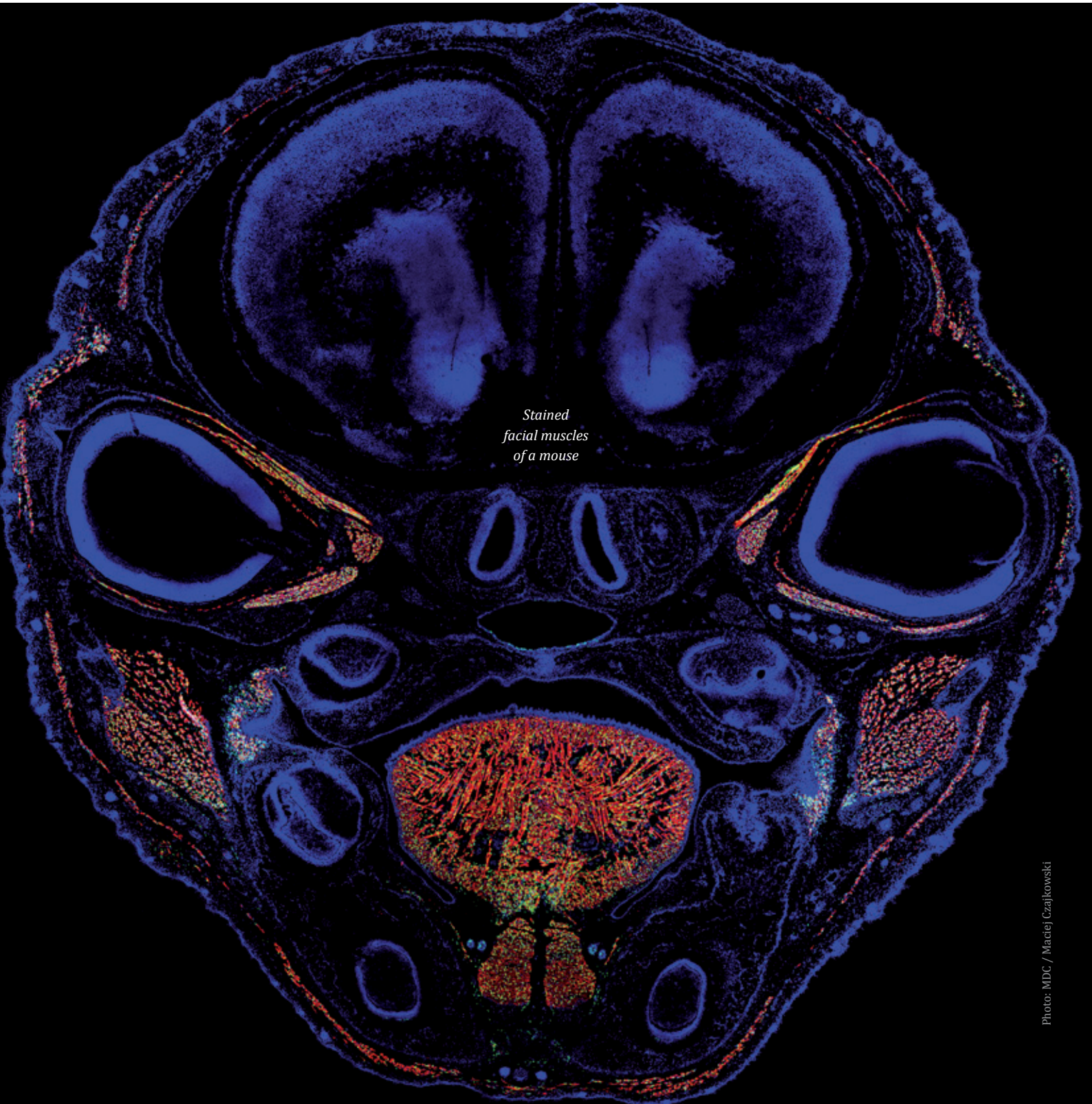
Photo: MDC / Diana Lehnhard

Stained muscles in the head of a mouse

Preclinical stem cell research

Good models needed

Before stem cell-based therapies can be tested on patients, they must first be extensively investigated in a preclinical development phase. Not all processes in the body can be simulated in the test tube or on the computer, so experiments on suitable animal models are essential. But stem cell technologies can also help to reduce the need for animal experiments in drug development. Cell cultures produced using pluripotent stem cells enable toxicology tests to be performed at an early stage, and multi-organ chips may soon make it possible to investigate the human body in miniature format.



Stained facial muscles of a mouse

Photo: MDC / Maciej Czajkowski

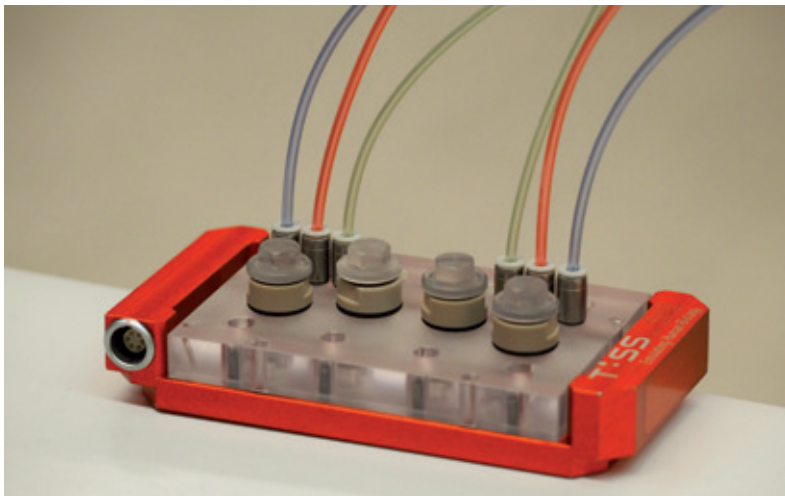
Any attempt to use cells as medical products involves dealing with highly complex, living biological systems – which makes working with them a special challenge. Before any clinical application can be trialed on humans, the safety profile and mode of action of the cell therapies must be thoroughly tested in living organisms. Animal experiments are controversial, but for the foreseeable future they will remain indispensable for biomedical research and application, because not all processes in the body can be simulated in the test tube or on the computer.

Innovative cell therapies differ fundamentally from conventional pharmaceutical substances in terms of their pharmacology and toxicology. This means that developers of cell-based medical products must draw up individual concepts for their products in order to provide the authorities with convincing data.

Small-animal models are of limited usefulness

But which animal model should be used to obtain the most informative results? The regulatory authorities favor what are known as homologous animal models. This means that the therapeutic effect of cells of a certain species is researched in a corresponding disease model – such as rat cells in rats with myocardial infarction. In other cases, heterologous models can be used – for example if human cell types are transplanted into rodents with a suppressed immune system or into "humanized" animals in order to prevent rejection.

Small-animal models – especially rodents such as rats and mice – are used in particular for early feasibility studies. "But in the later stages of development the use of appropriate large-animal models such as sheep or miniature pigs is unavoidable," says Thomas Braun, Director of the Max Planck Institute for Heart and Lung Research in Bad Nauheim. Braun, a developmental biologist, works exclusively in basic biomedical research; he studies muscle stem cells and the regeneration of heart muscle. Mice are some of his most important subjects



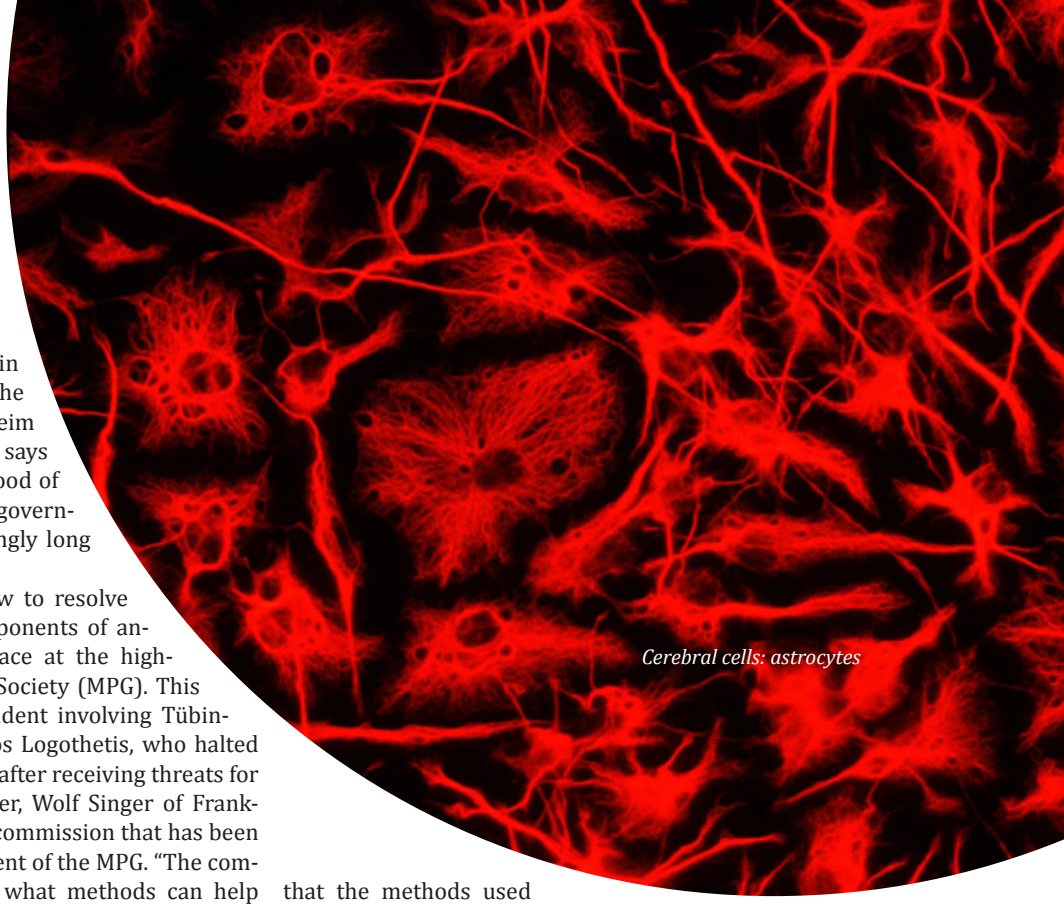
This Four-Organ-Chip contains an intestine, a liver, a kidney and a skin module.

Photo: TU Berlin_TissUse / Reyk Horland

New requirements bring extra bureaucracy

According to figures from the Federal Ministry of Agriculture, 2.8 million animals were used in scientific studies in 2014 – 870,000 of them in basic research and 333,000 in translational research. While the overall number of laboratory animals has fallen slightly, the number of transgenic rodents continues to rise – a trend that is ascribed to the steadily growing use of genetic engineering.

As a result of the new EU directive on the protection of animals used for scientific purposes, Germany's animal protection law has been amended. The new legislation came into force in 2013, with notable consequences. "The work involved in obtaining approval for animal experiments has increased dramatically," says Braun. "Regardless of whether we are using mice or zebra fish, we must now assess each individual transgenic stem for possible stress and in some cases obtain approval for an animal experiment from the authorities." Since breeding animals are also covered by this assessment, the overall documentation requirements



Cerebral cells: astrocytes

represent a significant increase in bureaucracy. To deal with this, the Max Planck Institute in Bad Nauheim has taken on extra staff. Braun says that the situation is creating a flood of paperwork, which the regional government offices take a correspondingly long time to process.
Meanwhile, deliberations on how to resolve the entrenched conflict with opponents of animal experiments are taking place at the highest level within the Max Planck Society (MPG). This was partly triggered by the incident involving Tübingen-based brain researcher Nikos Logothetis, who halted his experiments on apes in 2015 after receiving threats for months. Another brain researcher, Wolf Singer of Frankfurt, is heading an international commission that has been specially convened by the President of the MPG. "The commission is currently discussing what methods can help overcome the polarization," says Braun.

Alternatives to animal experiments

Although it might be desirable from an ethical point of view to replace all animal experiments with alternative methods of drug development, experts regard this as highly unfeasible in the foreseeable future. Nevertheless, in vitro models and simulations in silico are becoming increasingly informative and realistic; in some tests for the cosmetics industry they have already completely replaced animal experiments. Cell cultures enable toxicology studies to be carried out on potential drug candidates, especially when this involves testing their effect on heart and liver tissue in the Petri dish. Cardiotoxicity and hepatotoxicity are among the most common reasons why potentially promising substances are ruled out for further drug development.

Researchers investigating alternative methods use the principle of the 3Rs, developed in the 1950s. The 3Rs stipulate that the methods used should either avoid or replace the use of animals (replacement), minimize the number of animals used in experiments (reduction), or minimize animal suffering (refinement). The German Centre for the Protection of Laboratory Animals (Bf3R) was established in Berlin in 2015. It forms part of the Federal Institute for Risk Assessment (BfR) and is funded by the Federal Ministry of Agriculture. Bf3R focuses on methods that completely replace animal experiments – including stem cell-based cell culture tests such as the embryonic stem cell test. This uses mouse ES cells that are differentiated into heart muscle cells, nerve cells or bone cells. These cells can then be tested to discover whether substances might be toxic to embryonic development.

Elsewhere, too, scientists are refining stem cell-based methods for use in pharmacology and toxicology research. Pharmacologists led by Thomas Eschenhagen at the University Medical Center Hamburg-Eppendorf (UKE) have succeeded in growing iPS heart muscle cells in ordered,

Photo: ZEBET / Manfred Liebsch

Max Planck Institute for Heart and Lung Research
MPI-HLR

Max-Planck-Institut
für Herz- und Lungenforschung
W.G. Kerckhoff-Institut

The Max Planck Institute for Heart and Lung Research, located in Bad Nauheim, investigates developmental processes of organs in the cardiovascular system and the lung.

A second focus is molecular and cellular processes during the formation of diseases in heart, blood vessels and lung, including remodeling processes in these organs. Scientists at the institute search for new approaches to support repair and regeneration of the affected organs.

The MPI closely cooperates with universities in Frankfurt, Gießen and Marburg. It has become a major part of various federal and state excellence initiates and contributes to two "Gesundheitsforschungszentren".

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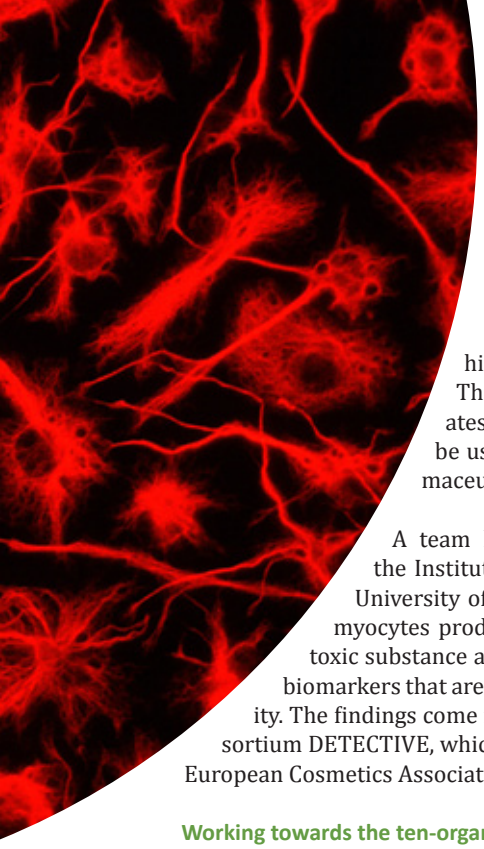


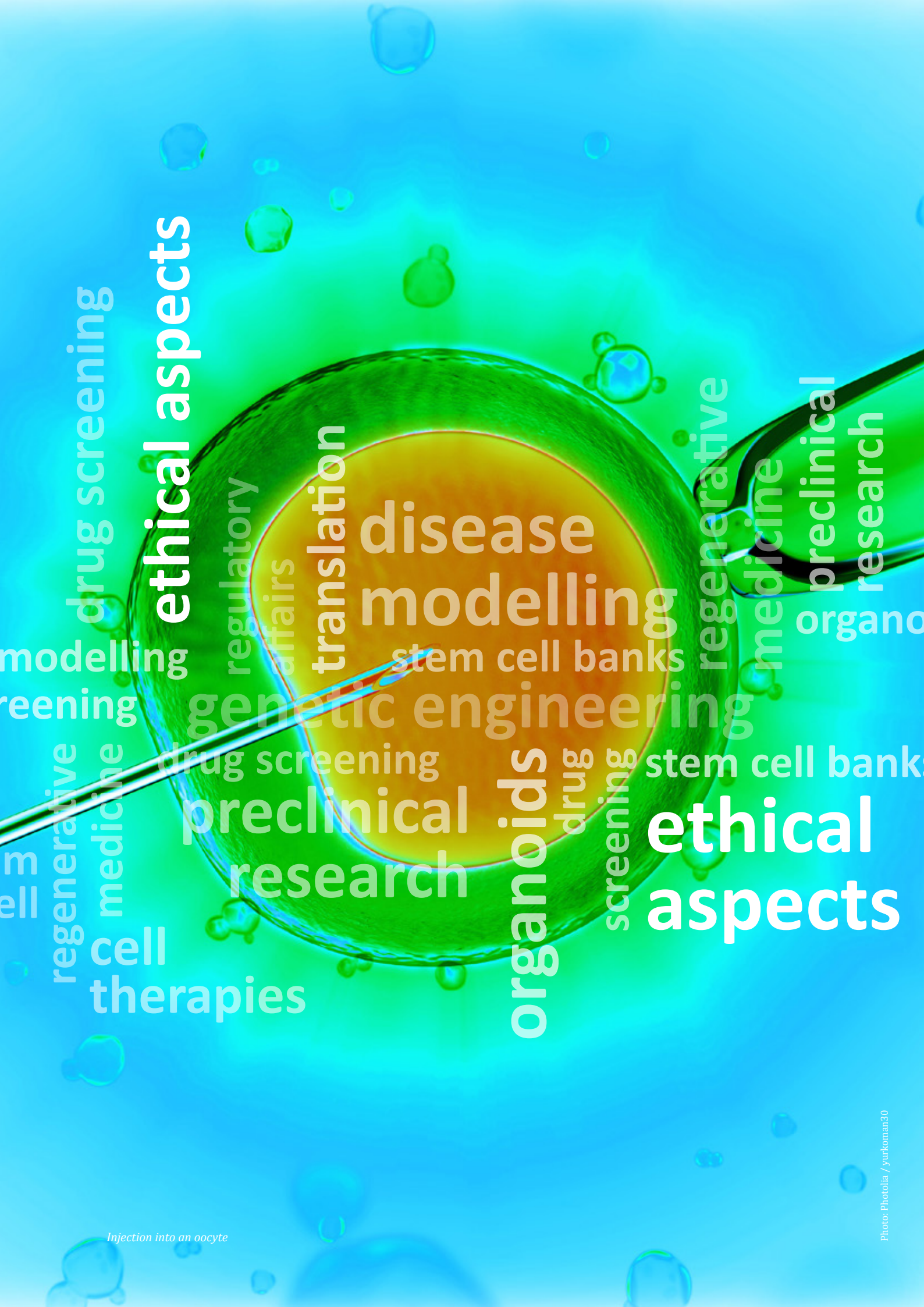
highly organized 3D networks. The team from Hamburg generates heart muscle strips that can be used to test the effect of pharmaceuticals on heart strength.

A team led by Jürgen Hescheler of the Institute of Neurophysiology at the University of Cologne has bathed cardiomyocytes produced by iPS techniques in a toxic substance and then identified molecular biomarkers that are characteristic of cardiotoxicity. The findings come from a project of the EU consortium DETECTIVE, which is supported in part by the European Cosmetics Association (Colipa).

Working towards the ten-organ chip

In vitro models still have their limits when it comes to assessing the efficacy and safety of substances. For example, they are unable to depict the interaction of organs. In an important new development, scientists are now trying to model various connected human organ systems on biochips. Biotechnologists led by Uwe Marx and Roland Lauster of the Technische Universität Berlin and the company TissUse are using iPS technology to engineer human organoids that mimic even the smallest functions of a particular organ. On the chip the human organs are shrunk by a factor of 100,000. The organoids thrive in small chambers on a plate the size of an object slide. The construct is supplied with a fluid-filled system of micro-channels that resembles the bloodstream. The first of these "multi-organ chips" were dual combinations of the skin and liver or the liver and nerve tissue. The most advanced product to come out of the Berlin project is currently a four-organ chip consisting of intestine, liver, kidney and skin modules. The tissue engineers hope to present a multi-organ chip with more then 10 organs in 2018. The research is supported by the BMBF within the GO-Bio-Program. The pharmaceutical industry already regards this miniaturized human test dummy as having great potential for the preclinical research of the future.

Text: Philipp Graf



Injection into an oocyte

Photo: Photolia / yurkoman30

Genome editing in the germline

Controversial cuts

In the hands of molecular biologists, genome editing is a powerful tool for the precise engineering of genetic material, something that scientists have long desired. But the revolutionary technology currently taking biomedical laboratories by storm is throwing up ethical and legal questions about the responsible limits of its use. 2015 was the year in which scientific academies worldwide launched an intensive debate on setting guidelines for the use of genome editing. Central to the discussion is the engineering of egg cells, sperm cells and newly created embryos in what are known as germline experiments. German stem cell researchers have stated their position in the debate.

Genome editing is now an established part of basic biomedical research. The designer nuclease system CRISPR/Cas9 took just three years to conquer biomedical laboratories (see GSCN Annual Magazine 14/15). This technology can be used to edit the genetic material in every conceivable type of cell – not just somatic cells but also germline cells, which include egg cells, sperm cells and embryos in the early stage of development. If their genome is edited, this produces a heritable modification that can be passed on to progeny. As exciting as the possibilities of genome editing may seem, the technique is not free from possible errors and risks. Last year saw the unfolding of a scientific debate on the medical applications of genome editing. While the debate was initiated primarily by researchers in the U.S., it was quickly taken up in Germany too.

Call for a moratorium

The debate was triggered by thought-provoking appeals from top researchers in the journals Science and Nature in March 2015. Leading molecular biologists and bioethicists called for a worldwide moratorium on human germline engineering in reproductive medicine. The International Society of Stem Cell Research (ISSCR) and the German Stem Cell Network (GSCN) also spoke out in favor of a moratorium on clinical germline experiments. The German academies of science likewise turned their attention to the issue. In July, the interdisciplinary Gene Technology Report research group at the Berlin-Brandenburg Academy of Sciences (BBAW) produced a highly regarded analysis of human genome engineering that elucidated the ethical and legal aspects of the new technology and interventions in the germline. The paper states that germline therapies and artificial modification of the genome in germline cells are in principle prohibited in Germany under the Embryo Protection Act – but there are a number of loopholes and exceptions. For example, purely in vitro experiments on human germ cells are permitted. There is also no ban on producing germ cells from iPS cells as the law does not cover this relatively new technology.

The authors of the BBAW paper support the call for an international moratorium on germline experiments. They hope that during the self-imposed suspension scientists

Max Planck Institute for Molecular Genetics
MPIMG

MPIMG

Research at the Max Planck Institute for Molecular Genetics (MPIMG) concentrates on genome analysis of man and other organisms to contribute to a global understanding of many biological processes in the organism, and to elucidate the mechanism behind many human diseases.

It is the overall goal of all MPIMG's groups to gain new insights into the development of diseases on a molecular level, thus contributing to the development of cause-related new medical treatments. In this context, stem cell research is gaining increasing importance. In particular, MPIMG researchers are working on a better understanding of gene regulation networks for tissue formation and homeostasis, as their dysfunction may result in numerous diseases

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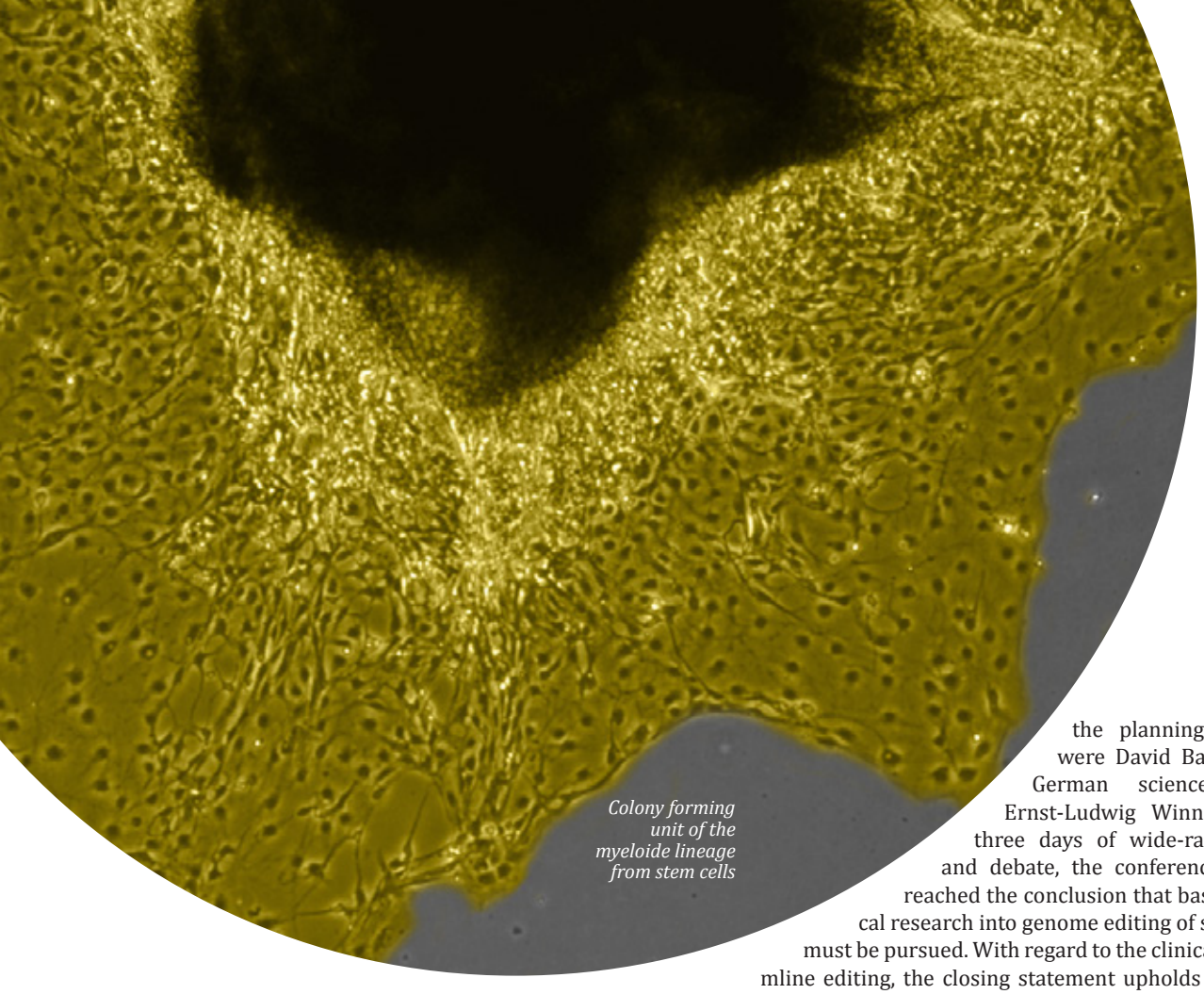

Colony forming unit of the myeloide lineage from stem cells

Photo: MHH / Mania Ackermann

and academics will engage in open, transparent and critical discussion of the experimental, ethical and legal aspects of germline therapy, elaborate the opportunities and risks of the technology for humans and nature, and draw up recommendations on future regulation. In September, the German National Academy of Sciences Leopoldina and the German Research Foundation (DFG) expressed similar views.

Genome engineering summit in Washington

The scientific debate reached an interim climax at the International Summit on Human Gene Editing held in Washington in early December. The conference was organized by the national science academies of the United States, the United Kingdom and China; among the members of the planning committee were David Baltimore and German science manager Ernst-Ludwig Winnacker. After three days of wide-ranging input and debate, the conference delegates reached the conclusion that basic and clinical research into genome editing of somatic cells must be pursued. With regard to the clinical use of germline editing, the closing statement upholds the existing reservations, stating that because of unresolved safety issues it would be irresponsible to proceed, especially given the lack of a broad societal consensus. However, the dialogue is set to continue, and some national academies have started to draw up guidelines on genome editing.

Stem cell researcher Albrecht Müller of the University of Würzburg has closely followed the recent debate on genome editing and has attended many related events, including the summit in Washington. Müller doubts that genome editing will ever be used to correct an unwanted mutation. "That will probably be done by means of pre-implantation diagnostics (PID)," he says. PID involves taking one cell from each of several embryos produced by in vitro fertilization and examining their genetic material. This enables embryos that are free from genetic defects to be iden-

Leibniz Institute for Zoo & Wildlife Research (IZW) in the Forschungsverbund Berlin e.V.

Evolutionary wildlife research for conservation

Leibniz-Institut für Zoo- und Wildtierforschung
IM FORSCHUNGSVERBUND BERLIN E.V.

The Leibniz Institute for Zoo & Wildlife Research (IZW) is an internationally renowned research institute of the Leibniz Association. With the mission of „understanding and improving adaptability" it examines evolutionary adaptations of wildlife and its resilience to global change, and develops new concepts and measures for conservation. To achieve this, the IZW uses its broad interdisciplinary expertise in evolutionary ecology and genetics, wildlife diseases, reproductive biology and management in a close dialogue with stakeholders and the public. The Department of Reproduction Management, headed by Prof Dr Thomas B Hildebrandt, develops cellular techniques for conservation. This new approach is an essential, promising option for highly endangered wildlife. For this purpose, the IZW builds up international networks on „cellular techniques", including international expert meetings of the world's leading scientists in the field of „cellular techniques", and develops new methods of securing and preserving wildlife tissue samples.

Leibniz-Institut für Zoo- und Wildtierforschung (IZW) im Forschungsverbund Berlin e.V.
Alfred-Kowalke-Straße 17 · 10315 Berlin
www.leibniz-izw.de

tified. "Genome editing for monogenic disorders makes little sense, and for polygenic ones it makes no sense at all," comments Müller. He reports that a possible application that was discussed in Washington is human enhancement, which involves modifying traits such as skin color. According to Müller, the conference participants were clear that such techniques are ethically highly controversial.

Further discussion needed

With regard to germline experiments in Germany, Müller believes that there must be a very clear boundary: no genetically modified embryo should be implanted in a womb. (Implantation is in any case banned under the Embryo Protection Act.) "But researchers should be able to use embryos left over from PID in their genome editing work," says Müller. He is of the view that the present discussion must be pursued by scientists and society at large. He maintains that "the solutions must come from science itself; the law shouldn't act prematurely, as happened with the Stem Cell Act. We are just at the beginning of the road here."

Hans Schöler, Director of the Max Planck Institute for Molecular Biomedicine in Münster, is highly critical of genome editing in the germline. He currently rejects intervention in human embryos, even for research purposes. "It doesn't seem to me at the moment that off-target effects can be controlled sufficiently for errors to be excluded," says Schöler. He points out that his own experiments on mouse cells have shown that even with recent versions of the CRISPR/Cas system a large number of faulty cuts in the genome still occur. In a germline experiment, an embryo is doubly stressed since its genes must be both checked and corrected. "In my view it would make more sense to test several embryos and transfer one that has no genetic defects." However, if the technique of genome editing were perfected and there was a valid reason for using it – instead of PID – Schöler says he might be able to accept it. However, he points out that this is nowhere near being the case at present. Nevertheless, he believes that now is the right time for public discussion of the ethically controversial matter of intervention in the human genome.

Text: Philipp Graf

Photo: Photolia / tarasov-vl

ESSAY: Untested stem cell therapies

Quacks and charlatans: Age-old adversaries, but no less dangerous!

by Ira Herrmann

The process for developing new drugs and treatment methods is usually lengthy and full of obstacles. In the interests of effectiveness and safety, research and validation are conducted in a way that allows them to be as internationally comparable as possible. By now, guidelines and standards on the manufacturing and testing of drugs and pharmaceutical products are subject to international regulations in order to ensure patient safety and the efficacy of new medicines. Nevertheless, some forms of treatment that are well established and fully approved today began life in "compassionate use" – i.e. outside controlled clinical studies. And there have always been those who have tried to bypass the lengthy clinical development stage so as to be able to offer new therapies faster. This secures them, at best, a shady chapter in medical history, and usually the only tangible results are their fatter wallets.

Regardless of the drug or procedure that needs to be tested, one of the constant challenges that developers and practitioners face is how to deal with patient expectations. This is a particularly heavy burden when it comes to treating patients with very limited options and, in the worst cases, low chances of survival. For some years now, certain providers have been taking advantage of the hype surrounding stem cells as some kind of miracle cure and exploiting the fact that there are currently no stem cell-based treatments and products available and that the legal framework for the use of stem cells is often sketchy. Yet the history of medicine has always been full of "miracle healers" and charlatans. What's more, loopholes in medical law are often knowingly accepted in the interests of freedom of therapy and the development of new fields.

So why is there such a fuss about offering unproven stem cell therapies? And is the reaction justified?

- Due to their special properties, stem cells have the potential to treat a wide variety of illnesses – including many widespread and/or currently incurable diseases. This potential creates expectations that science is unable to meet in such a short period of time (just as a reminder: the first isolation of human embryonic stem cells was achieved in 1998).

- Stem cell research is a young discipline with its roots in developmental and cell biology. Today, however, it needs knowledge input from other natural scientists, engineers and, above all, representatives of various medical and clinical disciplines. It has thus become a truly interdisciplinary scientific field. However, this interdisciplinarity also requires the establishment of a common language when discussing basics, methods and aims.

- The approval of stem cell-based therapies is subject to new and very particular legal conditions. So far, only very few authorizations have been granted worldwide, giving us very few precedents to learn from. In Europe, for instance, only six products have been approved under the EU Regulation on advanced therapy medicinal products (ATMPs), which came into force in 2008. So there is also still (pioneering) work to be carried out in this area by developers and regulatory authorities.

So we see that stem cell research is a young biomedical discipline that has great potential and capacity for innovation, but that is confronted with extreme expectations. These expectations need to be addressed and worked through in line with the principles of good scientific practice. It is advisable, therefore, to conduct dialogue with all stakeholders – dialogue that also allows for the public criticism of providers of unproven stem cell-based treatments. Not because quacks and charlatans are a new phenomenon, of course, but because stem cell research is such an important new field with the potential to solve the problems of an ageing society.

GSCN Annual Report

Boards

Executive Board

In accordance with Section 8(1) of the statute and rules of the German Stem Cell Network (GSCN) e.V., the Executive Board (presidium) consists of the Acting President (chairperson), the Senior President (first deputy chairperson), the Designated President (second deputy chairperson), the Treasurer, and the Assessor. In the reporting period (Sept. 2015 to Sept. 2016), the Executive Board is made up of the following members:

Acting President (Chair)	**Prof. Ulrich Martin** (Hannover Medical School) E-mail: *martin.ulrich@mh-hannover.de*
Senior President (1st Vice Chair)	**Prof. Thomas Braun** (Max Planck Institute for Heart and Lung Research, Bad Nauheim) E-mail: *office.braun@mpi-bn.mpg.de*
Designated President (2nd Vice Chair)	**Prof. Karl Lenhard Rudolph** (Leibniz Institute on Aging – Fritz Lipmann Institute [FLI], Jena) E-mail: *klrudolph@fli-leibniz.de*
Treasurer	**Dr. Michael Cross** (Leipzig University) E-mail: *michael.cross@medizin.uni-leipzig.de*
Assessor	**Prof. Frank Emmrich** (Fraunhofer IZI and Leipzig University) E-mail: *frank.emmrich@medizin.uni-leipzig.de*

Executive Board members: (from left): Karl Lenhard Rudolph, Thomas Braun, Ulrich Martin, Frank Emmrich, Michael Cross, Andreas Trumpp

Photo: GSCN

The Executive Board in 2015

The GSCN would like to thank the members of the 2015 Executive Board (Nov. 2014 to Sept. 2015). Andreas Trumpp, Active President in 2014, left the Executive Board as scheduled and has now been elected as a member of the Extended Board.

GSCN Executive and Extended Boards and Management

Extended Board

In accordance with Section 9(1) of the statute and rules of the German Stem Cell Network (GSCN) e.V., the Extended Board consists of up to 15 members. In the reporting period, the Extended Board is made up of the following members:

Prof. Oliver Brüstle (University of Bonn)
E-mail: *r.neuro@uni-bonn.de*

Dr. Tobias Cantz PD (Hannover Medical School)
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Dr. Micha Drukker (Helmholtz Zentrum München)
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Prof. Hartmut Geiger (Ulm University)
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Prof. Magdalena Götz (LMU Munich)
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Ira Herrmann (Stem Cell Network North Rhine Westphalia; Life & Brain since 1 Jan. 2016)
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(German Cancer Research Center Heidelberg)
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Prof. Albrecht Müller (University of Würzburg)
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Prof. Michael Rieger
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Prof. Hans R. Schöler
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Prof. Mathias Treier (Max Delbrück Center for Molecular Medicine Berlin)
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Prof. Claudia Waskow (TU Dresden)
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Photo: GSCN

Working group initiators

Scientific working groups

Pluripotency and Reprograming	Dr. Micha Drukker Prof. Hans Schöler Prof. Mathias Treier
Somatic Stem Cells and Development	Prof. Thomas Braun Prof. Elly Tanaka
Basic, Translational and Applied Hematopoiesis	Prof. Claudia Waskow Prof. Timm Schroeder (ETH Zürich) E-mail: *timm.schroeder@bsse.ethz.ch*
Stem Cells in Diseases (Cancer Stem Cells)	Prof. Thomas Brabletz (University Medical Center Freiburg) E-mail: *thomas.brabletz@uniklinik-freiburg.de* Prof. Andreas Trumpp
Stem Cells in Regenerative Therapies	Dr. Michael Cross Prof. Ulrich Martin
Stem Cells in Disease Modeling and Drug Development	Prof. Oliver Brüstle Prof. Karl-Ludwig Laugwitz (University Hospital Klinikum rechts der Isar, Munich) E-mail: *klaugwitz@med1.med.tum.de*
Computational Stem Cell Biology	Prof. Georg Füllen (Institute for Biostatistics and Informatics in Medicine and Ageing Research, Rostock) E-mail: *fuellen@uni-rostock.de* Prof. Ingo Röder (TU Dresden) E-mail: *ingo.roeder@tu-dresden.de*

Strategic working groups

Funding Programs and Policies	Prof. Ulrich Martin Prof. Albrecht Müller Acting GSCN President (ex-officio)
Promotion of Young Researchers	Prof. Hartmut Geiger (Ulm University) E-mail: *hartmut.geiger@uni-ulm.de* Prof. Jürgen Hescheler (University Hospital Cologne) E-mail: *j.hescheler@uni-koeln.de* Dr. Insa Schröder (GSI Helmholtz Centre for Heavy Ion Research) E-mail: *i.schroeder@gsi.de*
Public Engagement and Outreach Activities	Dr. Tobias Cantz PD Ira Herrmann
Patient Information (Stem Cell Therapies)	Dr. Gisela Badura-Lotter (Ulm University) E-mail: *gisela.badura@uni-ulm.de* Ira Herrmann
Clinical Trials and Regulatory Affairs	Dr. Zoltán Ivics (Paul-Ehrlich-Institut, Langen) E-mail: *Zoltan.Ivics@pei.de* Dr. Andreas Kurtz (BCRT Berlin), E-mail: *andreas.kurtz@charite.de* Prof. Torsten Tonn (Institute for Transfusion Medicine, Dresden) E-mail: *t.tonn@blutspende.de* Prof. Hans-Dieter Volk (BCRT Berlin) E-mail: *hans-dieter.volk@charite.de*
Stem Cell Technologies	Dr. Andreas Bosio (Miltenyi GmbH, Bergisch Gladbach) E-mail: *andreas.bosio@miltenyibiotec.de* Prof. Frank Emmrich

Facts and figures

Meetings

Executive Board meetings

The Executive Board of the GSCN regularly holds meetings and telephone conferences. These meetings are coordinated and organized by the Central Office. The following Executive Board meetings took place in 2015:

- Video conference (19 May 2015)
- Video conference (15 July 2015)
- Meeting (9 Sept. 2015) in Frankfurt am Main

Extended Board meeting

- 9 Sept. 2015 in Frankfurt am Main

General Assembly

- 10 Sept. 2015 in Frankfurt am Main

Overview of members in 2015

Total no. of members		**334**
Natural persons	Full members	189
	Junior members	116
Legal persons	Research institutes	17
	Companies with more than 20 full-time staff	4
	Companies with fewer than 20 full-time staff	7
	Partner societies	1
Membership cancelations in 2015		**32**
Members of the working groups		
Scientific working groups	Pluripotency and reprograming	184
	Somatic stem cells and development	145
	Basic, translational and applied hematopoiesis	64
	Stem cells in diseases (cancer stem cells)	136
	Stem cells in regenerative therapies	137
	Stem cells in disease modeling and drug development	185
	Computational stem cell biology	24
Strategic working groups	Funding programs and policies	124
	Career development	111
	Clinical trials and regulatory affairs	96
	Public engagement and outreach activities	60
	Patient information (stem cell therapies)	17
	Stem cell technologies	178

Last updated 31.1.2016

Institute members

- Berlin-Brandenburg Center for Regenerative Therapies (BCRT)
- Center for Regenerative Therapies Dresden (CRTD)
- German Cancer Research Center (DKFZ), Heidelberg
- Fraunhofer Research Institution for Marine Biotechnology (Fraunhofer EMB), Lübeck
- Fraunhofer Institute for Molecular Biology and Applied Ecology (IME), Aachen
- Fraunhofer Institute for Production Technology (IPT), Aachen (from 2016)
- Fraunhofer Institute for Cell Therapy and Immunology (Fraunhofer IZI), Leipzig
- Institute of Reconstructive Neurobiology, University of Bonn
- Institute for Stem Cell Research and Regenerative Medicine, Düsseldorf
- Leibniz Institute on Aging – Fritz Lipmann Institute (FLI), Jena
- Leibniz Institute for Zoo and Wildlife Research in the Forschungsverbund Berlin
- Max Delbrück Center for Molecular Medicine (MDC), Berlin-Buch
- Max Planck Institute for Heart and Lung Research (MPI-HLR), Bad Nauheim
- Max Planck Institute for Molecular Genetics (MPIMG), Berlin
- REBIRTH Cluster of Excellence, Hannover Medical School
- Collaborative Research Center SFB 873, Centre for Organismal Studies, Heidelberg University Hospital
- Tissue Engineering and Regenerative Medicine (TERM), University Hospital of Würzburg
- Universitätsklinikum Erlangen, Department of Molecular Neurology, Bavarian Research Network ForIPS – Induced Pluripotent Stem Cells (from 2016)

Company members

- AMS Biotechnology (Europe) Ltd.
- Biological Industries
- Eppendorf AG
- Essen BioScience Ltd.
- Hexcell Berlin GmbH
- HI-STEM gGmbH
- Thermo Fisher Scientific
- Macopharma Int. GmbH (from 2016)
- PELOBiotech GmbH
- PeproTech GmbH
- Takara Bio Europe S.A.S.

Partner societies

- German Society for Transfusion Medicine and Immune Hematology (DGTI) e.V..

GSCN General Assembly

Eighty-eight members attended the third General Assembly of the GSCN, held on 10 Sept. 2015 during the 3rd Annual Conference in Frankfurt am Main. The minutes of the assembly and the presentation that formed part of it can be downloaded from the members' area of the website. The Executive Board and the Extended Board were re-elected in the online elections of August 2015 (see above) after the auditors officially discharged the previous board members.

General Assembly 2015

Photos: GSCN

Activities in 2015

2015 was a busy year for the GSCN, with numerous events, new formats, and interesting workshops and conferences. On the one hand, the GSCN is a members' association with a focus on networking; on the other, it promotes communication with the public and policymakers. Below is a summary of the activities undertaken by the GSCN in both of these areas.

The network

The GSCN Annual Conference is the largest assembly of stem cell researchers. At the **3rd International Annual Conference of the GSCN** in Frankfurt am Main, 400 scientists came together to exchange ideas, develop partnerships, initiate new projects, and bring each other up to date on the latest research. Networking is about making contacts, developing collaborative projects, establishing friendly relationships, and linking new research to new faces and institutions. These networks are of ongoing importance to current and future projects. The GSCN has also created contact platforms on the international level. For example, it developed a new format called the **WunderBar Evening** for the **ISSCR** Annual Meeting in Stockholm on 23 – 26 June 2015. Around 100 members and friends attended the event held on the roof terrace of the Clarion Hotel Sign at the close of the conference day. The evening proved to be a success despite the cool Scandinavian temperatures, with great midsummer views over Stockholm, a fun and relaxed atmosphere, delicious finger food and drinks, and stimulating conversation.

The **GSCN Meet-Up Hub** took place the following afternoon in the **ISSCR exhibition hall**. As well as GSCN members, the event also attracted many international colleagues for an inspiring one-hour meet-up in the middle of the conference. "I'm very satisfied with both events; we achieved our goal of creating spaces for people to network in a pleasant and animating environment," said Daniel Besser, Managing Director of the GSCN. **Twenty-one junior scientists** who had been granted **Travel Awards** by the GSCN working groups attended the meet-up – and their response was particularly enthusiastic. "For me, it was great to attend the GSCN Meet-Up Hub. I met several scientists who were working in Germany. We discussed future directions of the field of pluripotency and reprograming as well as potential collaborative works," said award winner Kee-Pyo Kim of the Max Planck Institute for Molecular Biomedicine in Münster.

Scientists at all stages of their careers are involved in the GSCN network. This year, the GSCN organized the first round of the **GSCN Awards** to raise awareness of the work carried out by specific groups in these various stages and to recognize outstanding achievements. For each of the awards, there is a submission process that includes stating the reasons for nomination, convening a selection committee, and

Participants of the Non-PI-Meeting in Bonn

plenty of work on the part of the jury. The following scientists received awards for their outstanding and impressive research work:

- The GSCN Young Investigator Award was granted to **Dr. Julia Ladewig** of the Institute of Reconstructive Neurobiology at University Hospital Bonn.

- The GSCN Female Scientist Award was presented to **Prof. Magdalena Götz** of the Institute of Stem Cell Research at Helmholtz Zentrum München. Götz is also chairs the Department of Physiological Genomics at LMU Munich.

- The GSCN Publication of the Year Award went to **Jichang Wang** and **Dr. Zsuzsanna Izsvák** from the Mobile DNA research group at the Max Delbrück Center for Molecular Medicine (MDC) in Berlin-Buch for their article "Primate-specific endogenous retrovirus-driven transcription defines naïve-like stem cells", which was published in the academic journal *Nature* (Wang, J. et al., 2014, Nature, doi:10.1038/nature13804).

The GSCN Awards ceremony took place at the Presidential Symposium held at the GSCN Conference in Frankfurt and featured talks by the three award-winners, who all felt deeply honored to have received the awards (see Conference report). For the GSCN, the awards ceremony represents a commitment to promoting science policy.

In 2015, the GSCN again granted **Travel Awards** to enable talented junior scientists to take part in various conferences and summer/winter schools. Thanks to the Travel Awards, Onur Basak (Hubrecht

Institute, Utrecht, Netherlands), Debojyoti Chakraborty (BIOTEC, University Hospital Carl Gustav Carus, Dresden), Christina Galonska (Broad Institute of MIT and Harvard, Cambridge, USA), Sarah Konze (Hannover Medical School), and Miha Modic (Helmholtz Zentrum München) were able to attend the GSCN Annual Conference in Frankfurt. All Travel Awards were funded by GSCN company member Eppendorf AG. The GSCN continued to **promote young talent** and provide financial, subject-related and logistical support through the first **non-PI meeting** in Bonn (20 April 2015), where 18 young scientists came together for an exchange of ideas in a series of lectures and discussions. "All the participants were enthusiastic about the atmosphere of the meeting and the possibility of sharing their experiences with one another. They encourage the GSCN to continue the concept of non-PI meetings in the future," said participants Adele Marthaler and Henning Kempf. The non-PI meeting took place in the run-up to the 8th International Meeting of Stem Cell Network North Rhine-Westphalia in Bonn (21 – 22 April 2015). After the meeting, the GSCN was the main sponsor of the **6th Bioinformatics and Stem Cells Satellite Workshop** (22 – 23 April 2015), a one-day event organized by Georg Füllen, initiator of the Computational Stem cell Biology working group. The strategic working group on **Career Development** explored a completely new field by organizing a workshop on **"Scientists in Management"** in Darmstadt (17 – 18 Nov. 2015). It is especially useful for scientists to master soft skills like strategic and management competencies at an early stage in their careers. "The response to the workshop was extremely positive," said Insa Schröder, initiator of the working group on Career Development. In addition, the GSCN presented information materials at the **World Conference on Regenerative Medicine** in Leipzig (21 – 23 Oct. 2015; see News) and various other meetings and conferences, such as the **IGLD Meeting** at the Max Delbrück Communications Center in Berlin (12 – 14 March 2015) and the 4th International Conference on **Strategies in Tissue Engineering (SITE)** in Würzburg (10 – 12 June 2015). The GSCN played a key role in establishing a network of German stem cell core units in a bid to stimulate discussion and improve communication between scientists. The goal of the new network is, first and foremost, to create and standardize joint quality protocols and methods to safeguard the pluripotent state of hiPSCs.

Communication

Cultivating contacts, collaborating, and communicating in a network are important ways of passing on information. The GSCN makes use of various communication channels. At the conference the annually updated **mobile app GSCN Navigator** enables participants to shape their visit to the conference to suit their personal interests. The GSCN also provides information and news in German and English on its website *www.gscn.org*. In 2015 the website attracted more than 24,700 visits from 15,000 users (2014: 18,000 visits from 9,500 users). Visits have thus increased by 28% and the number of users by 37%. The news column on the website's home page highlights the latest developments in the field – a service that is appreciated by many users. The **GSCN Newsletter** goes out by e-mail and the **Annual Magazine**, which focuses on different topics each year, is sent out to members in the mail. In 2015 the magazine concentrated on stem cell technologies, considering Germany from the perspective of the various core institutions involved. The 2015 annual magazine was very well received and a record 1,000 copies were distributed.

At the first GSCN annual conference in Berlin in 2013, members expressed a wish for an internal, web-based communication platform: in 2015 this was created in the form of the **GSCN Humhub.** This social Intranet has not yet become established as a fully-fledged **professional and social stem cell network** – but of course this is the goal. Each of the scientific and strategic working groups has its own forum; members are assigned to their own working groups but can also participate in other groups. This is intended to provide a very simple, forum-like means of communication that enables members to discuss issues online, exchange information, to post details of conferences, workshops, talks and publications, and to debate these. As a bonus, **promotional codes for conferences, grants** or other member benefits will appear first on Humhub. 2015 was the launch year – the GSCN Humhub network should really get underway in 2016.

Internationally, the GSCN worked closely with **EuroStemCell** in 2015. At a wide-ranging European **workshop in Brussels** (18 – 19 Feb. 2015), the EuroStemCell team set out new objectives, and topic groups were formed to drive forward this European information portal and promote the working groups behind the new funding application to the European Commission. In 2015 most of the work

Photos: GSCN

Poster exhibition in the Urania, Berlin

took place behind the scenes, but in 2016 and 2017 this major European partner will launch many new projects in a new guise – this will include a relaunch of the website, which the GSCN is helping to design. The relationship between the GSCN and EuroStemCell is fruitful for both organizations – for example, the GSCN used the Edinburgh meeting factsheets on various diseases (*www.eurostemcell.org*) to produce a **colorful poster display** that is proving popular at events.

These communicators' meetings also promote networking on international stem cell research. The international collaboration was continued at the meeting in **Edinburgh** on 12 – 13 Nov. 2015. Its subject was "Train the Trainers," and it provided many examples of how information on stem cell research can be communicated in a way that inspires interest in people of all ages and educational backgrounds. Nationally, the GSCN organized a similar meeting with its **Communication on Stem Cell Research** group. Held in Berlin on 27 – 28 April 2015, the meeting combined a workshop on public affairs with networking and the development of new projects. Like last year's meeting in Hannover (which we reported on), the event generated many good ideas and helped to develop useful contacts between the science communicators of the various research institutions. One specific outcome was the defining of the group of institutes that will organize **UniStem Day** on 11 March 2016 as a **European day of action on stem cell research**. A thousand school students are expected to take part in a day of concentrated activities covering all aspects of stem cell research – including talks, films, games and guided tours.

School students were the target audience of GSCN events at the MINT400 forum at the Max Delbrück Center (MDC) in Berlin (12 - 13 Feb. 2015 and 4 - 5 Feb 2016), at the Science Day at the Robert-Havemann-Gymnasium in Berlin-Karow (19 Nov. 2015) and at the debate on stem cells and ethics at Haus Kreisau youth education center (29 Jan. 2015). The MDC in Berlin puts on regular informational careers events for young scientists wanting to learn more about new professional fields. At the knowledge management careers fair on 20 Nov. 2015 Daniel Besser explained the duties of the managing director of a scientific network and discussed his work with the young scientists who attended.

The GSCN organized games and talks for interested members of the public at the **Long Night of the Sciences** in Berlin on 13 June 2015. Following on from the Frankfurt conference, the GSCN held a panel discussion on the Westend campus at which facilitator Stefanie Seltmann (DKFZ) and panel members Thomas Braun (MPI for Heart and Lung Research), Hubert Serve (oncologist, hematologist, University Hospital Frankfurt), and Andreas Zeiher (cardiologist, University Hospital Frankfurt) debated the latest laboratory and hospital research, taking as their subject the use of stem cells in the treatment of heart attacks and leukemia. The **latest GSCN films about Andreas Zeiher and Hubert Serve** were also shown. Like the **GSCN films about Magdalena Götz, Andreas Trumpp and Anthony Ho** from 2014, these have now been

MINT-Students spend a „stem cell day" with Daniel Besser

Photos: GSCN

GSCN panel discussion in Frankfurt: Thomas Braun, Hubertus Serve, Stefanie Seltmann and Andreas Zeiher debate about possible applications of stem cell therapies.

translated into English and are proving to be very popular items on the EuroStemCell website. They have the highest click rates on the European website. The films can be found on the GSCN website at: *www.gscn.org/en/RESOURCES/GSCNMovies.aspx*.

The year's events drew to a close on 2 Dec. 2015 with the **GSCN panel discussion** on "Modern cell therapies – Using stem cells to treat heart and blood disorders" at the **Urania** in **Berlin**, where the audience enjoyed screenings and a panel discussion with Claudia Waskow (hematologist, TU Dresden), Daniel Besser (Managing Director, GSCN), and Carsten Tschöpe (cardiologist, Charité and Berlin-Brandenburg School for Regenerative Therapies).

At the **World Health Summit** in Berlin on 11 – 13 Oct. 2015 the GSCN again put the subject of stem cells on the agenda by organizing its own session. A panel of high-profile international speakers discussed the future applications and potentials of stem cells, thus bringing the research field to the attention of an audience of medical experts and policymakers from all over the world.

The GSCN is also active in social media with a growing number of followers. The GSCN Central Office regularly receives enquiries from teachers, students, patients and journalists, which are answered with the help of scientists. The GSCN conference, in particular, prompts nationwide coverage in print and online media.

Finances

The GSCN is a non-profit organization funded by **membership subscriptions and grants from the BMBF**. Under Section 4 of its statute, the level of subscriptions is set by rules adopted at the General Assembly. Subscriptions are detailed on the GSCN's membership form.

The business year is the calendar year. Subscriptions are due at the start of the business year. The Executive Board is responsible for producing the annual accounts and submitting them to the General Assembly. Details of the **association's finances** are provided at the General Assemblies.

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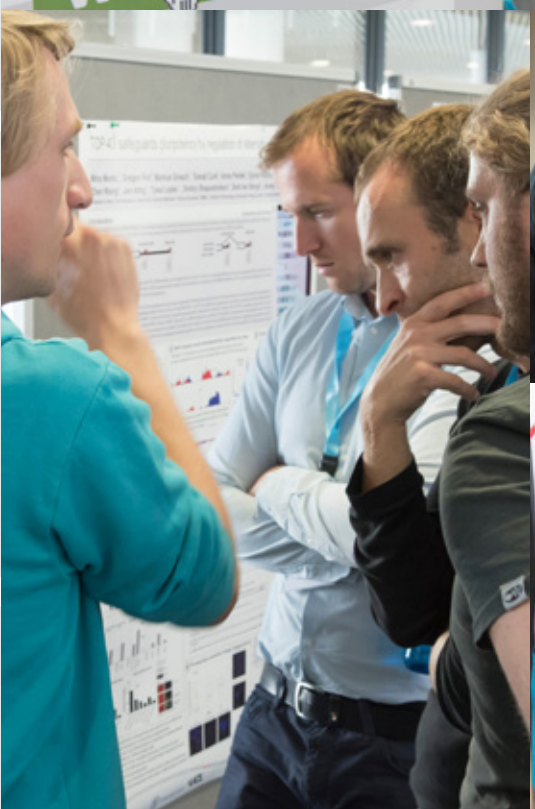

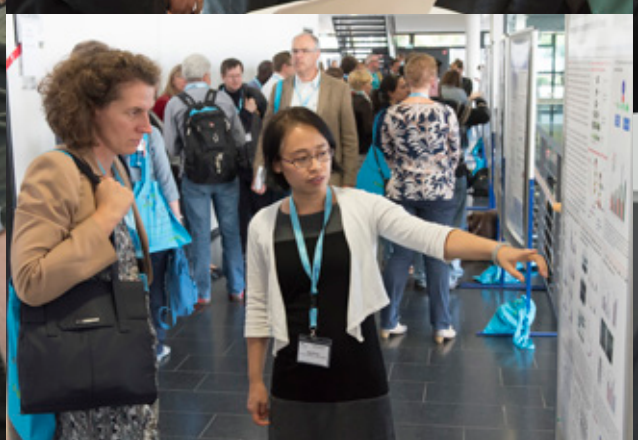

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