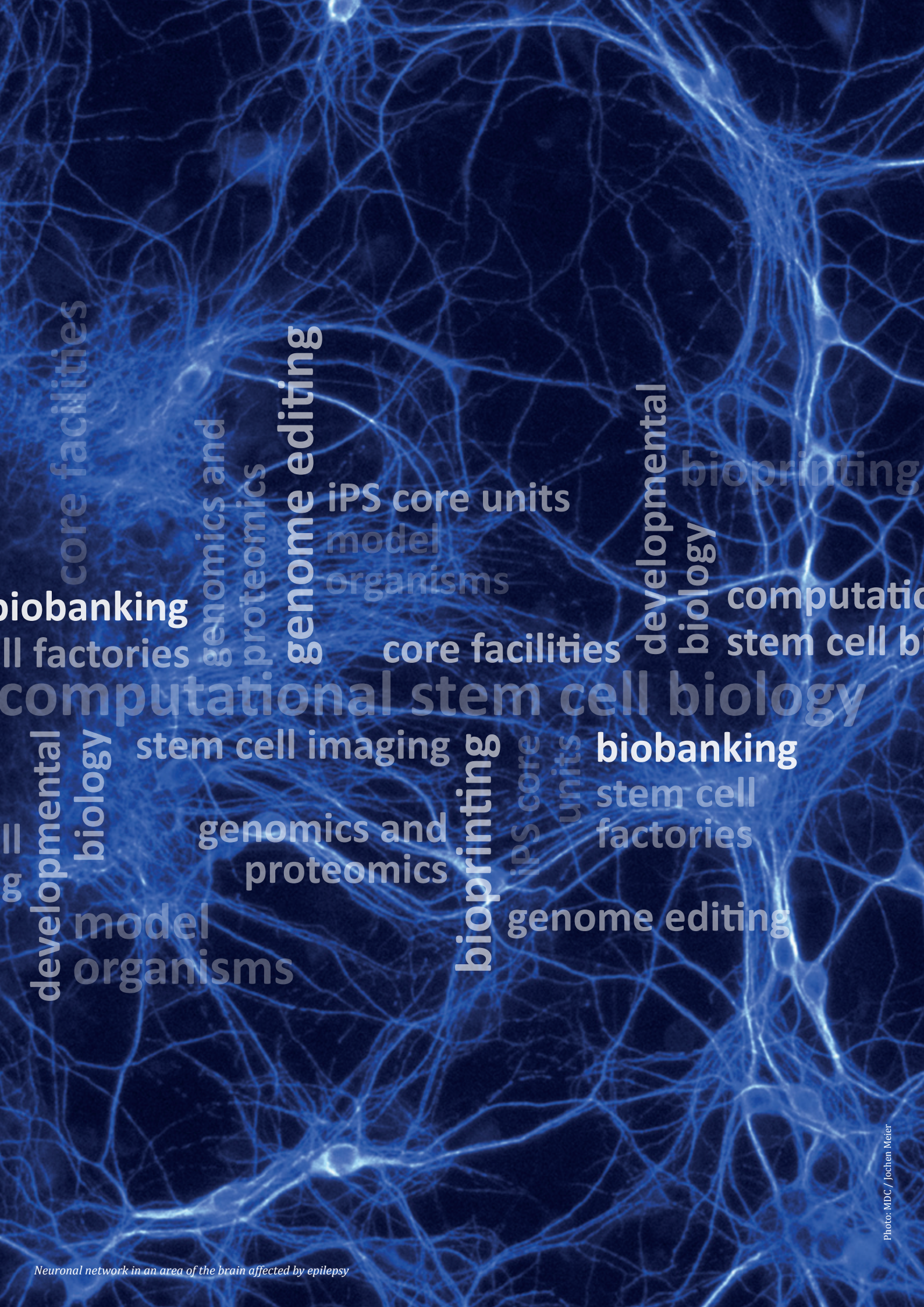


Neuronal network in an area of the brain affected by epilepsy

Photo: MDC / Jochen Meier

Archiving stem cells

Cell treasures from a catalog

Pluripotent stem cells are important resources for the medicine of the future. If the vast range of existing stem cell lines is to be tracked and made available for practical use, these lines must be tested, cataloged and stored in a central location. Cell archives thus become important treasure troves for stem cell researchers. Using state-of-the-art cryogenics, researchers from Germany are involved in the development of systematic online catalogs and biobanks.

It is in the nature of stem cells that they have permanent characteristics: once obtained, pluripotent cells can be cultivated and propagated almost indefinitely. Stem cell lines are therefore valuable biological resources that are predestined to be shared among researchers and users and made available in central collections. This is particularly true of embryonic stem cells (ES cells), the acquisition and use of which is governed by different legal conditions in different countries. In addition, the technique of reprogramming has led to the engineering of induced pluripotent stem cells (iPS cells) on a significant scale in recent years. A major issue for science and industry in this context is the quality and comparability of engineered cell lines. This has given rise on the European level to a number of initiatives with German participation.

Stem cell register: Online catalog of ES cells

To obtain human ES cells, the embryos must usually be destroyed. This ethically problematical step triggered intense and controversial debate in the early years of this decade. In Europe, this resulted in a patchwork of stem cell regulations, with conditions covering the entire spectrum from liberal to restrictive.

The European Human Embryonic Stem Cell Registry (hESCreg) was created in 2007 to provide an overview of existing human ES cell lines from European laboratories. "In setting up this public information portal, the European Commission particularly wanted to create transparency and place research on a sound ethical foundation," says Andreas Kurtz, one of the hESCreg coordinators at the Berlin-Brandenburg Center for Regenerative Therapies (BCRT) at the Charité. Other partners are the Stem Cell Bank of Barcelona at the CMR[B] and the UK Stem Cell Bank in South Mimms, north of London.

The data catalog records where the cells originated and are stored, and describes their biological and "ethical" profile. This enables stem cell researchers to answer questions such as: "Where is there a suitable cell line?"; "Are the cells actually pluripotent?"; "Were they obtained under conditions that are ethically acceptable for my research?"

The number of entries in the stem cell register has grown quickly – and it includes data from outside Europe. "We are now the leading global register of pluripotent stem cell lines," states Kurtz. He estimates that there are more than 2,000 ES cell lines in the world, of which around 800 are now recorded in hESCreg.

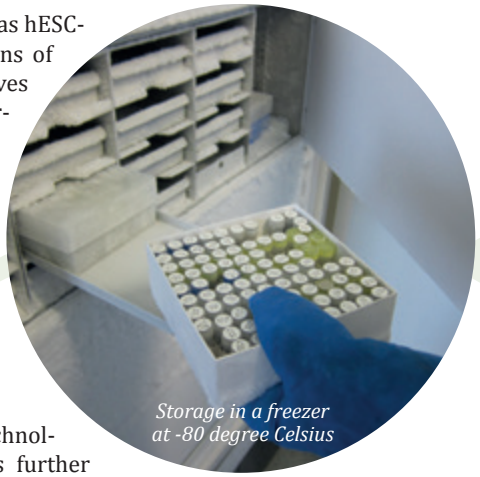
The most important global directory of pluripotent cells

For a time, the data portal had to manage without EU funding, but since 2013 EU money has again been contributing to development of the stem cell register. This has enabled its task spectrum to be significantly expanded. For example, iPS cell lines obtained from patients with a specific disorder are now recorded. From an ethical perspective, this poses additional challenges. "The cell donors are still alive. Their consent forms must therefore be available, and sensitive data must be appropriately protected," explains Kurtz. At the German Stem Cell Network (GSCN), Kurtz heads a strategic working group "Clinical trials and regulatory affairs".

Stem cell researchers are already benefiting from the changes at hESCreg: on the occasion of the 2nd GSCN annual conference in Heidelberg in November 2014 the completely revised website (www.hescreg.eu) went online. The search templates of the new version enable researchers to comb through the cell lines in more detail than before. "And external users can now also enter cell lines online," says Kurtz. Moreover, hESCreg is to take on a further function. According to the plans of the EU Commission, cell lines will not in future be considered for EU project funding unless they are included in hESCreg. The coordinators of the stem cell register are also to assume a monitoring role in the future. "We are currently developing a tracking system for this purpose," says Kurtz, who is based in Berlin where, together with three members of staff, he has particular responsibility for coordination, IT and information management of the online platform.

Biobank boom

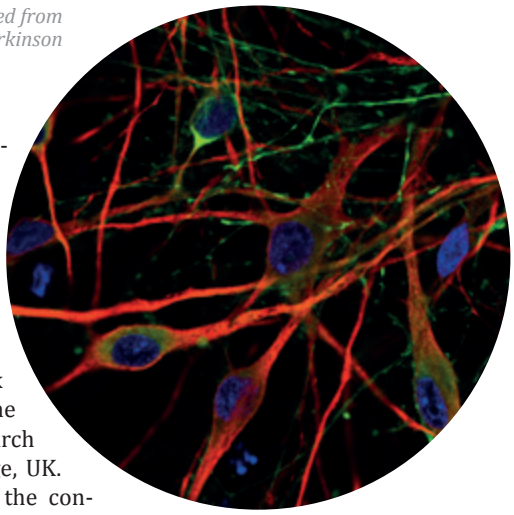
Stem cell registers such as hESCreg are simply collections of data; the cells themselves are stored in refrigerators at individual research laboratories. This makes exchange difficult, especially as the quality of the cells may vary widely. The logistic requirements stretch many laboratories to their limits.



Storage in a freezer at -80 degree Celsius

Photo: Fotolia / pp77

The advance of iPS technology in laboratories has further



Dopaminergic neurons from iPS cells derived from a patient with Morbus Parkinson

complicated the situation. Reprogramming makes it possible to generate human cell lines that carry a patient's genome. This lays the foundation for patient-specific disease models. Tracking down the molecular causes of a disease requires a large number of cell lines from as many patients as possible. For their drugs tests, pharmaceutical researchers are already dreaming of creating large patient groups – available at any time in the form of iPS cells in the Petri dish.

In consequence, researchers from academia and industry are calling ever more loudly for central cell archives or biobanks. These provide an infrastructure for testing and storing cells in accordance with defined standards. The systematically cataloged lines can then be sent all over the world in response to orders. In Europe, the Innovative Medicines Initiative (IMI) has backed the creation of two research alliances that plan to set up central biobanks for iPS cells. IMI is a public-private partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA). German stem cell researchers are heavily involved in both organizations.

The EBiSC European iPS bank

An IMI consortium launched in 2014 plans to set up a central European Bank for induced Pluripotent Stem Cells (EBiSC) over the next three years to systematically archive well-characterized iPS cells from all over Europe. It envisages a collection of 1,000 defined and characterized cell lines from patients with specific diseases, tailored to the needs of the pharmaceutical industry and health research.

"An ambitious target: 1500 cell lines from 500 patients with various diseases"

These requirements include sufficiently large cell quantities – 100 million cells per line are planned – that are ready to use in drug screenings. Once it has been established, both the scientific community and industry will have access to the non-commercial biobank, which will eventually support itself financially. EBiSC, which has a budget of €35 million, is a consortium of 26 organizations coordinated by pharmaceutical corporation Pfizer. Seven German partners are involved.

The central biobank will be set up on the Babraham Research Campus in Cambridge, UK. A special feature of the consortium is a "mirror bank" that will store a complete equivalent of the EBiSC collection as a backup. The mirror bank is located in the Saarland in Germany. The Fraunhofer Institute for Biomedical Engineering (IBMT) is setting up the necessary infrastructure in the town of Sulzbach, where a team led by Julia Neubauer is responsible for freezing the cells, for automating cell cultivation, and for the logistics of the biobank. The IBMT researchers use a technique that involves carefully cooling the stem cells to minus 130 degrees Celsius: the stem cells can remain adherent to the culture surface if they are frozen with nitrogen gas. In the Fraunhofer facility the stem cells are then stored in cryotanks with special protective hoods. The hoods prevent other samples being affected when cell samples are removed and ensure that the cool chain remains unbroken. In other respects, too, the cryopreservation technology used is state of the art: both the automated freezing process and the storage are computer-controlled. The EBiSC researchers have already deposited the first iPS cell lines in their cell bank; it is anticipated that potential users will be able to start requesting cell lines in 2017.

StemBANCC: Focus on neurological disorders and diabetes

An European IMI consortium is behind another five-year project on iPS cells, StemBANCC, which was launched back

Photo: University of Lübeck

Berlin-Brandenburg Center for Regenerative Therapies
BCRT

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

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in 2012. StemBANCC is coordinated by Swiss pharmaceutical company Roche; the leading academic partner is the University of Oxford. Nine of the 35 partners are from Germany.

The consortium, which has a budget of €55 million, aims to establish high-quality iPS cell lines from healthy subjects and patients that can be used for biological disease models and toxicology tests. "The focus is on widespread diseases such as neuronal and neurodegenerative disorders and diabetes," says Christine Klein of the Institute of Neurogenetics at the University of Lübeck. Her team coordinates patient recruitment for the consortium; they work with other clinical centers in Europe to select patients and obtain skin samples. The target is ambitious: the consortium partners plan to collect skin samples from 500 patients with the various diseases and generate 1,500 cell lines from them. Progress varies on different fronts: "At our location we have already completed recruitment of Parkinson's patients and control patients," says Klein. The iPS cells will be generated and characterized in the UK under standardized conditions. They will also be cataloged there and deposited in a biobank so that they will be available to researchers all over the world in the future.

A special biobank with cells from Lübeck

At Lübeck University Hospital, a center for research into rare diseases, neurogeneticist Christine Klein and her team have exclusive access to patient material that is of great interest for health research and disease models in the Petri dish. Moreover, her team has built up considerable expertise in iPS technology in recent years. To utilize this potential, Klein and five colleagues have developed a business idea that is now coming to fruition: the company iPS-HL is due to be launched in Lübeck this spring. "We won't only have a special selection of iPS cell lines from patients available but will also be able to offer customers the improved end products, such as differentiated cell types," explains Klein. From the many enquiries she receives it is clear that the majority of researchers want to get going on relevant cell types straight away.

Whether for use in cell-based tests or in innovative therapies, standardized and reliable sources of stem cells are essential in regenerative medicine. The biobanks and registers that are now being set up all over the world play a crucial role in this.

Text: Philipp Graf