

TITELTHEMA

## REBIRTH sets learning in motion

### SCIENCE

BOOST-2 results in potential proteine therapy

### NEW SPIN-OFF

Boost worth millions for MHH spinoff company

### INNOTRUCK

REBIRTH on an important mission



# Latest Publications

## Heart: cell enrichment using small molecules

Despite significant progress in generating heart muscle cells (cardiomyocytes) from human pluripotent stem cells (hPSCs), the targeted generation of pure subtype-specific cardiomyocytes remains challenging. Previous studies in mouse PSCs suggested the induction of pacemaker-like cells by the small molecule EBIO, an established modulator of Ca<sup>2+</sup> activated K<sup>+</sup> (SK) channels. In this publication, however, Jara-Avaca and colleagues demonstrate that EBIO does not induce cardiomyogenic differentiation in PSCs, but mediates selective cardiomyocyte survival and subsequently enrichment in a time- and dose-dependent manner. Moreover, EBIO-treated cardiomyocytes display action potentials that are shortened overall, which may support the development of more subtype-specific human cardiomyocytes for basic research and pharmacological studies.

### Publication

Jara-Avaca, M., Kempf, H., Ruckert, M., Robles-Diaz, D., Franke, A., de la Roche, J., Fischer, M., Malan, D., Sasse, P., Solodenko, W., Drager, G., Kirschning, A., Martin, U., and Zweigerdt, R. (2017). EBIO Does Not Induce Cardiomyogenesis in Human Pluripotent Stem Cells but Modulates Cardiac Subtype Enrichment by Lineage-Selective Survival. *Stem Cell Reports*. Epub: 2017/01/12.

## Journal special edition on lung regeneration

REBIRTH researchers Matthias Ochs and Christian Mühlfeld, who were invited to be guest editors, have put out a special edition of the journal *Cell and Tissue Research* titled 'Development, Remodeling and Regeneration of the Lung'. The publication contains 24 review articles on key aspects of the thematic area described in the title, written by renowned national and international experts.

### Publication

Mühlfeld C, Ochs M. Development, remodeling and regeneration of the lung: coping with the structural and functional challenges of breathing. *Cell and tissue research*. 2017;367(3):407-11. Epub 2017/01/17.

## Improved vectors for iPSC cells

Genetic correction of patient-specific induced pluripotent stem cells (iPSCs) using retroviral vectors could lead to improved treatment of monogenic diseases. However, the current bottleneck is epigenetic vector silencing. REBIRTH researchers systematically compared vectors from different retroviral genera, promoters and their combination with ubiquitous chromatin-opening elements, and several pseudotypes. In the process, they identified the lentiviral vector with the CBX3.EFS promoter as a promising promoter and vector configuration for sustained/long-term modification of human iPSCs and their progeny.

### Publication

Hoffmann D, Schott JW, Geis FK, Lange L, Muller FJ, Lenz D, Zychlinski D, Steinemann D, Morgan M, Moritz T, Schambach A. Detailed Comparison of Retroviral Vectors and Promoter Configurations for Stable and High Transgene Expression in Human Induced Pluripotent Stem Cells. *Gene Ther*. 2017;24(5):298-307. Epub 2017/03/28.

## Study on humanized mice

Humanized mice, which have been continuously improved in the past decade, are used to study human immune responses *in vivo*. They are immune-deficient animals transplanted with human haematopoietic stem cells, capable of developing into human T and B cells. When, in collaboration with colleagues at the Fraunhofer ITEM, the Stripecke Lab used humanized mice as a 'pharm/tox' model to preclinically test a cell vaccine, an unexpected observation was made. Some of the mice developed a skin inflammation caused by interaction of activated human memory T cells with mouse macrophages. This pathology must be factored in when testing biomedical products in these complex human-mouse chimeric models.

### Publication

Sundarasetty B, Volk V, Theobald SJ, Rittinghausen S, Schaudien D, Neuhaus V, Figueiredo C, Schneider A, Gerasch L, Mucci A, Moritz T, von Kaisenberg C, Spineli LM, Sewald K, Braun A, Weigt H, Ganser A, Stripecke R. Human Effector Memory T Helper Cells Engage with Mouse Macrophages and Cause Graft-Versus-Host-Like Pathology in Skin of Humanized Mice Used in a Nonclinical Immunization Study. *Am J Pathol*. 2017;187(6):1380-98. Epub 2017/04/23.

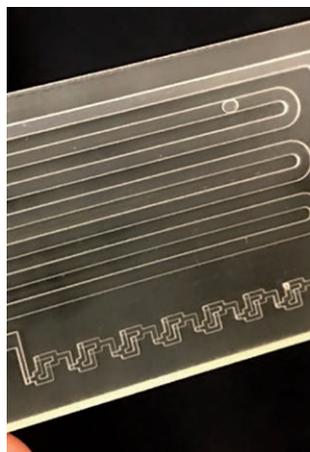


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## REBIRTH sets learning in motion

REBIRTH active school: medical scientists launch exercise programme for pupils

Children and adolescents are exercising less and less. To boost awareness of preventive action among parents and in schools, the REBIRTH Cluster of Excellence is launching a two-year motion study called 'REBIRTH active school' in cooperation with the scheme 'Bewegte, gesunde Schule Niedersachsen' ('Active and healthy schools in Lower Saxony'). The first examinations and training units took place at a participating Hannover primary school (Grundschule Groß-Buchholzer



Kirchweg) in early April 2017, since then the medical team has extended the study to include Kronsberg's integrated comprehensive school and three other schools in the Lippe district: Geschwister-Scholl-Schule, Weerth-Schule and Bachschule. By the summer holidays, the team had already examined almost 350 children. The first training units are planned for the autumn term.

Whereas preschoolers generally get enough exercise, physical activity declines dramatically when they start school. Some families and schools are insufficiently aware of this situation and its negative consequences, the lack of exercise being associated not only with a heightened risk of overweight, cardiovascular and metabolic diseases, but also leading to diminished learning capacity and, at worst, mental ill health. "Over the



next two years, we want to positively influence the health and the (age-appropriate) physical development of more than 400 Year 2 and Year 5 pupils, while also boosting the performance of some 120 teachers,” says REBIRTH coordinator Professor Axel Haverich, director of MHH’s Department of Cardiothoracic, Transplantation and Vascular Surgery (HTTG) and the study’s initiator. He plans to achieve this by means of regular exercise units. The children will receive exercise instructions from sports scientists, assisted by teaching staff, several times during the school day – and this includes lesson time. At least half of these physical activities are to take place during classes, with ‘maths and movement’ exercises, as well as coordination and stamina training in various subjects.

“The aim of these exercise units is to improve the children’s subsequent concentration and hence enhance both their learning and performance capability,” comments Professor



Uwe Tegtbur, director of MHH's Institute of Sports Medicine. So that the effect of these measures can be properly gauged, the pupils will be divided into an observation group and an intervention group during the first year. The study will be bookended by thorough medical check-ups for both groups, performed by MHH paediatricians. "These will include various cardiovascular parameters, with individual physical performance assessed. This will involve ultrasound scans of the heart and vascular system, as well as tests of pulmonary function and bicycle ergometry. We'll obtain other important information from blood, saliva and urine testing," explains Professor Anette Melk, a senior physician (Oberärztin) at MHH's Centre for Paediatrics and Adolescent Medicine. The medics will also be looking at dental status. "Inflammation of the gums is one of the commonest types of infection worldwide and, via the blood, influences the development of cardiovascular diseases," says Professor Meike Stiesch, director of MHH's Department of Dental Prosthetics and Biomedical Materials Science. "And sporting activity has a positive impact on chronic inflammatory processes."

## Exercise helps cells regenerate

An important aspect of the study is the measurement of telomere length. Telomeres (gene sequences at the end of our chromosomes) are an indicator of the cells' regenerative potential. There is a close link between their length and healthy lifestyle: active sports enthusiasts have longer telomeres. Conversely, the length of telomeres may be reduced

by negative factors. In a French study involving almost 800 children, those who are overweight and inactive already have markedly shorter telomeres. Teams who conducted two previous studies with MHH staff showed that regular endurance sport has a positive effect on telomere length – and hence on cell regeneration.

## Exercise benefits both body and mind

"Major changes in the lives of adolescents, such as an increase in sedentary leisure activities or greater take-up of full-day and extracurricular services, highlight the pressing need to make their day-to-day lives more active. The 'Active and healthy schools in Lower Saxony' scheme takes the role of exercise very seriously, and so it supports 'REBIRTH active school' as a way of injecting more physical activity into our children's everyday experience", says Hermann Städtler, who is in charge of the Lower Saxony schools project. Nicole Dreyer, head teacher at the Groß-Buchholzer Kirchweg primary school, adds, "Exercise equally benefits both the body and the mind. Perhaps the findings of this medically oriented study will contribute towards its being more strongly integrated into the learning process than before."

The study is supported by the Braukmann-Wittenberg Foundation to the tune of 1.3m euros, as well as by the REBIRTH Cluster of Excellence and from 'Niedersächsischen Vorab'.

### About this publication

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# Cellular therapy: expectations unfulfilled

Following a major heart attack, patients' risk of developing a persistent weakening of the heart muscle (i.e. cardiac insufficiency) remains just as high as it was – despite cellular therapy. Based on a trial entitled BOOST ('Bone marrow transfer to enhance ST-elevation infarct regeneration'), successfully completed in 2004, researchers at Hannover Medical School (MHH) have now published the findings of the follow-up study, BOOST-2, in the renowned *European Heart Journal*. In both trials, the physicians treated patients with these individuals' own bone marrow cells during the first week after a serious heart attack. These cells were infused into the reopened coronary artery and thus directly into the infarcted region. It was hoped that they would locally release growth factors that enhance the healing process. However, "in contrast to the first BOOST study, we did not observe any significant improvement in heart function during the BOOST-2 trial," reports principal investigator Professor Kai Wollert of MHH's Department of Cardiology and Angiology and the REBIRTH unit on Secreted Factors and Non-cell-based Strategies for Cardiac Regeneration. "We would now no longer recommend such therapy in this form."

The first BOOST study involved the treatment of 60 patients between 2002 and 2003 at MHH's Department of Cardiology and Angiology (at the time still headed by Professor Helmut Drexler). The outcome was a marked improvement in cardiac function, specifically by 6%. In 2006, to corroborate these findings, the team led by Professor Wollert and Professor Gerd Meyer launched a randomized and placebo-controlled double-blind trial, BOOST-2, at nine German centres and a Norwegian one. It was funded by the German Research Foundation (DFG) and the Alfred Krupp von Bohlen and Halbach Foundation. Although the therapy was (as in BOOST) well tolerated, BOOST-2 saw a mere 1% improvement in heart function - not, in other words, the hoped-for result. "We assume this is due to the fact that

treatment of these patients has improved in the intervening years. Today, myocardial infarction sufferers are treated earlier and receive more advanced stents, as well as more effective medication," adds Professor Johann Bauersachs, the present-day head of MHH's Department of Cardiology and Angiology.

However, the study was not in vain. When the researchers analysed the patients' bone marrow cells for factors that



*Professor Johann Bauersachs and the initiators of the BOOST-2 trial, Professor Kai Wollert and Professor Gerd Meyer (from left) in the Cardiac Catheter Laboratory.*

may enhance the recovery process following a heart attack, they discovered a previously unknown growth factor, specifically myeloid-derived growth factor (MYDGF). "One advantage is that such growth factors – unlike the patients' own cells, whose quality differs between individuals – can be developed in a standardized manner, like drugs can," Professor Wollert says. The medical scientists have now joined forces with a partner in industry to focus on taking MYDGF from bench to bedside.

#### *Publication*

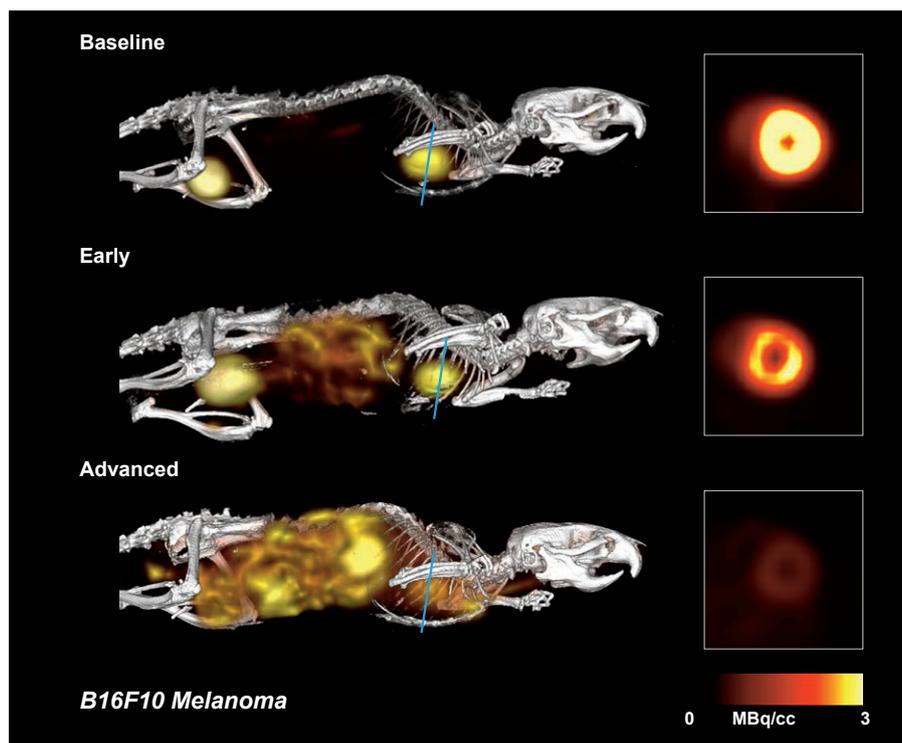
*Wollert KC, Meyer GP, Muller-Ehmsen J, Tschope C, Bonarjee V, Larsen AI, May AE, Empen K, Chorianopoulos E, Tebbe U, Waltenberger J, Mahrholdt H, Ritter B, Pirr J, Fischer D, Korf-Klingebiel M, Arseniev L, Heuft HG, Brinckmann JE, Messinger D, Hertenstein B, Ganser A, Katus HA, Felix SB, Gawaz MP, Dickstein K, Schultheiss HP, Ladage D, Greulich S, Bauersachs J. Intracoronary Autologous Bone Marrow Cell Transfer after Myocardial Infarction: The Boost-2 Randomised Placebo-Controlled Clinical Trial. *Eur Heart J*. 2017. Epub 2017/04/22*

# Tumours: insulin protects the heart

runs short of energy. As the tumour constantly absorbed sugar from the blood, the pancreas was not prompted to release insulin.

The multidisciplinary team analysed blood samples and found it was indeed the case that much smaller quantities of insulin were detectable in the blood of seriously ill tumour patients as well as mice with advanced-stage mela-

noma or colon carcinoma than in healthy individuals. When mice with tumours were continuously treated with low doses of insulin, the researchers noted that the heart and other organs (such as skeletal muscle) began absorbing more glucose again. But less sugar was available to the tumour, and its growth decreased. This is because the tumours in this study lack insulin receptors and their uptake of glucose is independent of insulin. Insulin is, however, also a growth factor, one of whose jobs is to promote muscle development and prevent extensive muscle wasting. "It became apparent that additional uptake of insulin in diseased mice led not



People with advanced-stage cancer frequently suffer from wasting syndrome (with muscle loss and emaciation), which may also compromise the heart and lead to its failure. A group of researchers headed by Professor Denise Hilfiker-Kleiner (REBIRTH unit on Endogenous Regeneration of the Heart) and Professor Frank Bengel (REBIRTH unit on Radionuclide Molecular Imaging) discovered that these cancer sufferers have an insulin deficiency that affects the entire body. In mice, too, individuals with advanced skin or intestinal cancer had only low levels of insulin throughout the organism. It was also observed that, in terminal patients, the heart shrinks. Using the imaging technique PET-CT (positron emission tomography / computed tomography), the team led by Professor Bengel looked to see where in the body the blood glucose ends up. The scans clearly showed that the tumour takes all the sugar for itself. Not enough is supplied to the heart, so it

only to enhanced glucose uptake by the heart but also reduced loss of muscle – especially the heart muscle – and thus improved cardiac function," Professor Hilfiker-Kleiner says. "It's conceivable that the continuous administration of insulin at a low dosage, as a treatment complementing the actual cancer therapy, is a way of preventing heart failure and reducing tumour growth – provided, of course, that the tumour doesn't respond to insulin." The investigators, who also belong to Clinical Research Group 311, published their findings in the journal *JCI Insight*. Dr James T. Thackeray, Stefan Pietzsch and Dr Britta Stapel share lead authorship of the study.

#### Publication

Thackeray JT, Pietzsch S, Stapel B, Ricke-Hoch M, Lee CW, Bankstahl JP, Scherr M, Heineke J, Scharf G, Haghikia A, Bengel FM, Hilfiker-Kleiner D. Insulin Supplementation Attenuates Cancer-Induced Cardiomyopathy and Slows Tumor Disease Progression. *JCI Insight*. 2017;2(10). Epub 2017/05/19.



## Technion Award 2017

Professor Denise Hilfiker-Kleiner, REBIRTH Unit on Endogenous Regeneration Mechanisms of the Heart, who has had the honour of receiving one of two Science Prizes awarded by the German Technion Society (DTG e.V.). The German Friends of the Israel Institute of Technology (a public research university in Haifa, Israel) presented these awards at the Leibnizhaus in Hannover on 6 March 2017.

The prizes, each worth 5,000 euros, are presented biannually to researchers who have achieved scientific excellence and who, by virtue of close collaboration, have also specifically promoted joint efforts between German and Israeli scientists. "I'm extremely grateful to my Israeli colleagues at Technion, particularly Professor Ofer Binah, for what has now been more than 15 years of highly productive teamwork. And I really feel honoured to have been selected for this important scientific award," says Professor Hilfiker-Kleiner. She has worked with Israeli researchers from Technion on two major collaborative projects. This research has focused on signal mechanisms that play a crucial role both in damage to, and in the regeneration and recovery of, cardiac muscle.

# Particulates and their effect on transplanted hearts

Changes to coronary blood vessels are among the most frequent causes of death following a heart transplant. And particulate exposure is an added risk factor.

Changes to the coronary arteries following heart transplantation (HTx) are highly prevalent. In the long term, transplant vasculopathy (TVP) causes problems far more often than an acute rejection response. Moreover, according to the Registry of the International Society for Heart and Lung Transplantation, TVP is one of the commonest causes of

## What are particulates?

Atmospheric particulate matter consists of particles that differ in size and composition. Three groups are recognized ( $< 0.1 \mu\text{m}$ ,  $0.1\text{--}2.5 \mu\text{m}$  and  $2.5\text{--}10 \mu\text{m}$ ), with only the latter two subject to legal requirements and routine monitoring.

death among heart transplant patients. In recent years, a number of observational studies in different countries have found particulate exposure to have a negative impact in terms of cardiovascular disease. A correlation was found with the risk of heart attack, cardiac arrest and total subsequent mortality. The same has been shown for stroke patients. To date, however, exposure to particulate matter as a post-organ transplant risk factor has been investigated only for lung transplantation.

A team lead by Professor Christoph Bara (a REBIRTH member from MHH's Department of Cardiothoracic, Transplantation and Vascular Surgery) has now explored the relationship between particulate exposure and the development of changes in the coronary arteries of transplanted hearts. They looked at 105 heart transplant patients, treated at MHH's transplant outpatient clinic in 2015, who had had this surgery between five and 29 years previously. The phy-

## How might particulates exacerbate disease?

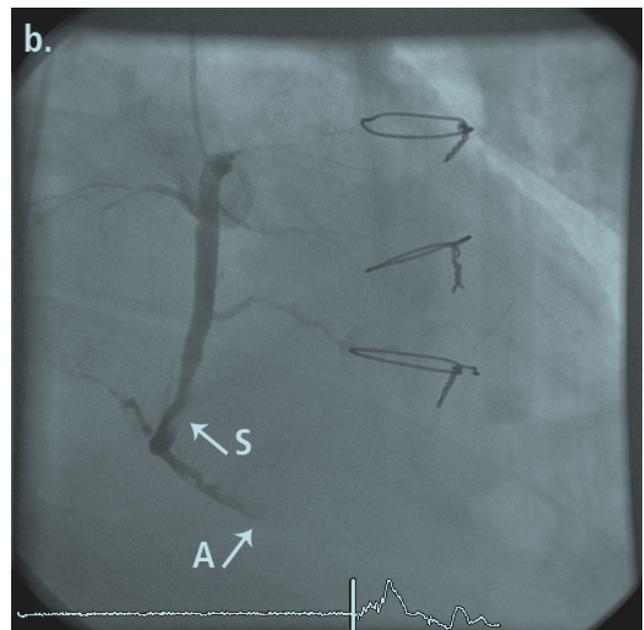
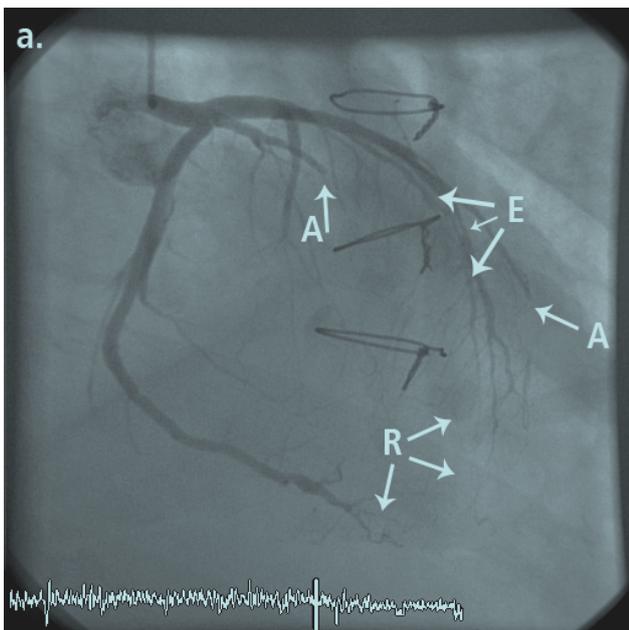
The influence of particulates on the development of various diseases has been the subject of increased investigation in recent years. The pathomechanism is thought to be the alveolar uptake of particulates in leu-

cocytes which, for their part, may in some cases provoke effects on the endothelium of a wide range of tissue types: inflammatory responses followed by endothelial dysfunction, inhibition of fibrinolysis and activation of thrombocytes. They may also promote the development of arteriosclerosis and the progression of atherosclerotic plaque. In this way, constant exposure on the part of organ transplant patients could also stimulate an immune response to foreign tissue.

sicians used coronary angiography to diagnose TVP in 50 patients; it was ruled out in another 55. They found that, in the patient group with lowest particulate exposure, considerably fewer individuals developed TVP than in the group with the highest exposure levels. And, the higher the exposure, the earlier TVP occurred. "We demonstrated a clear link between TVP development following a heart transplant and the patient's exposure to particulate matter, irrespective of known risk factors such as the number of earlier rejections, CMV infection, arterial hypertension, diabetes and body mass index," reports Professor Bara. "Our

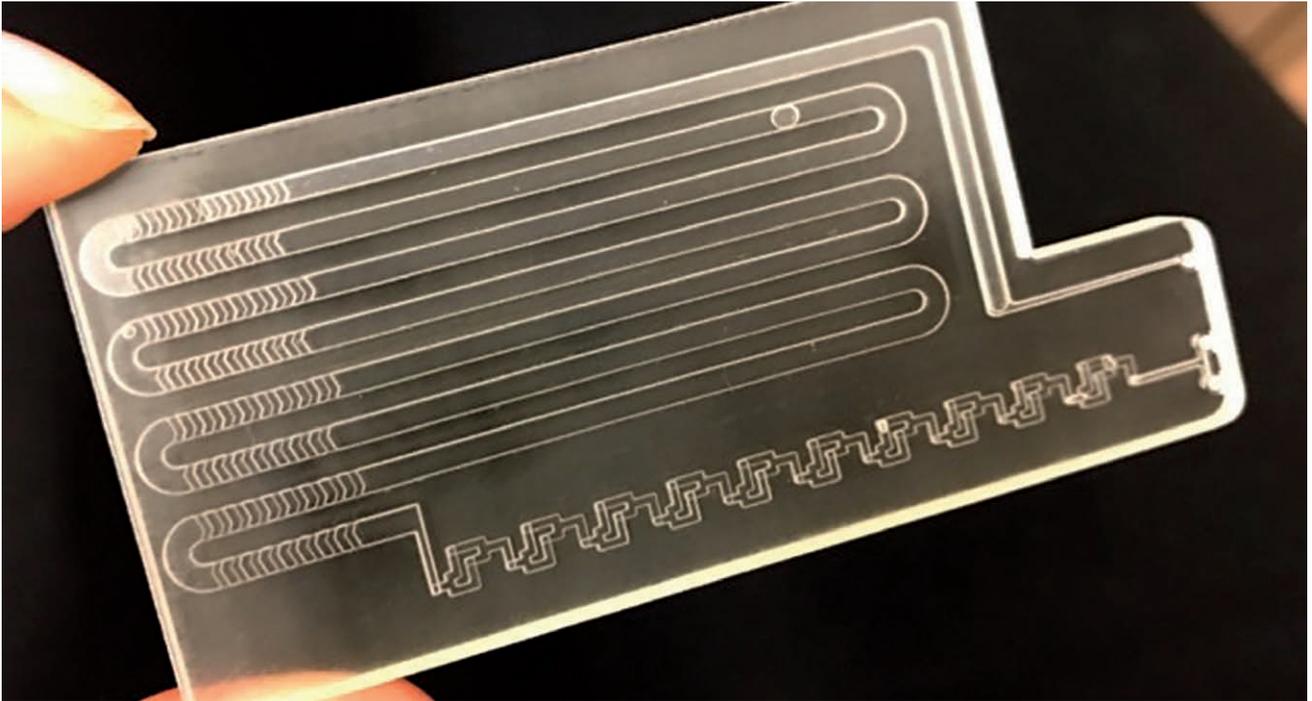
findings highlight the need for further studies." Larger patient cohorts are to follow, as are detailed factoring-in of long-term changes over time in particulate levels, geographical differences in particulate exposure and any relocation by the patient, in order to confirm or refute the initial suspicion. The team published their findings in the *Deutsches Ärzteblatt*.

Publication  
DOI: 10.3238/PersKardio.2017.03.31.07



### Coronary angiography of a 33-year-old male patient

27 months post-HTx: Left (a) and right (b) coronary artery; advanced TVP with vascular interruption affecting the ramus intermedius, the ramus interventricularis anterior and posterior (A); stenosis of the right coronary artery (S); diffuse, long constriction of diagonal branches (E); and rarefaction of peripheral vessels (R).



**From 3D design to 3D printing:**  
The system consists of a split-and-recombine (SAR) micromixer and an incubation channel with integrated herringbone structures that ensure efficient mixing of a cell suspension.

by Janina Bahnemann

## New lab-on-a-chip systems

Microfluidics and the development of 'lab-on-a-chip' (LOC) systems form the basis for a wide range of uses in medical engineering, biotechnology, biology and chemistry. In particular, the great potential for application inherent in the manipulation of cells and other biological samples in microstructured systems has generated much interest, and provides new ways of testing dynamic response to various external influences. System miniaturization has allowed reproducible experimental conditions to be created that enable, for instance, a native, physiologically favourable cell environment to be maintained. However, the complex process involved in fabricating traditional microsystems means such systems are highly expensive and time-consuming to produce.

In recent years, three-dimensional (3D) printing has attracted growing scientific attention. Remarkable technical ad-

vances now make it possible for high-definition (HD) structures to be printed on a scale of only a few micrometres. These developments can also be brought to bear in microsystem technology, and are being increasingly exploited for 3D printing of microfluidic prototypes and single-use systems. Employing an innovative, HD 3D printer, the researchers produce LOC prototypes for use in cell culture technology. This work, at the Institute of Technical Chemistry (ITC), is overseen by REBIRTH area manager Professor Thomas Scheper.

One early application is that of microsystems which allow continuous and flexible manipulation of animal cells. Devices called micromixers can be used, for example, to mix cells gently and efficiently with a desired reagent within a very short period. A major advantage of 3D-printed microsystems over traditional methods of production is that desired prototypes can be printed within only a few hours of the 3D design and modelling process. This means that modifications needed in order to optimize these systems can be rapidly implemented and tested.



*Professor Thomas Thum and Cardior's CEO  
Dr Claudia Ulbrich.*

## Boost worth millions for MHH spinoff company

**Cardior Pharmaceuticals GmbH receives 15 million euros  
for rapid development of new therapeutic options for  
heart patients.**

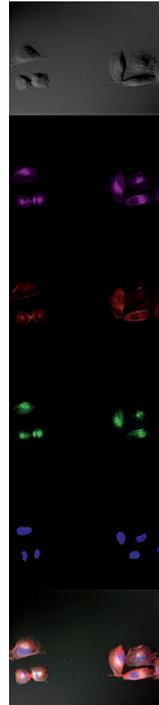
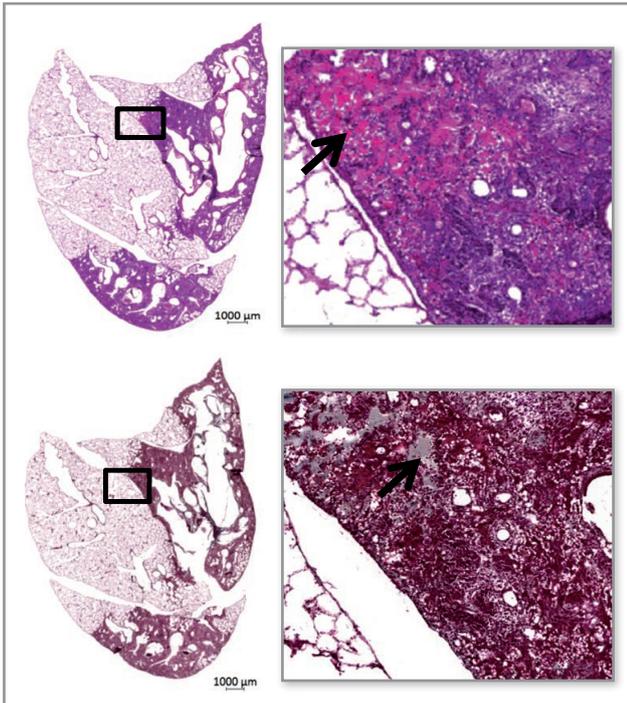
A great translational success story for the REBIRTH Cluster of Excellence and Hannover Medical School (MHH): Cardior Pharmaceuticals GmbH, a recent MHH spinoff company, has received a total of 15 million euros from five investors. LSP (Life Sciences Partners) will be supporting the biotechnology firm created in 2016, along with Boehringer Ingelheim Venture Fund (BIVF), Bristol-Myers Squibb (BMS), BioMedPartners (with their new BioMedInvest III Fund) and High-Tech Gründerfonds (HTGF).

"We use what are known as non-coding ribonucleic acids (RNAs) to diagnose and treat heart conditions such as heart failure," says Professor Thomas Thum, who is Cardior's founder, head of MHH's Institute of Molecular and Translational Therapy Strategies (IMTTS), and leader of the REBIRTH unit on miRNA in Myocardial Regeneration. In order to prevent or reduce cardiac insufficiency – i.e. heart failure – the heart's muscle cells are enabled to reverse abnormal remodeling processes and to work normally once more. "Our therapeutic agents influence specific non-coding RNAs that control the growth and contractile ability of cardiac muscle cells, and which are instrumental in causing heart failure," Professor Thum explains. He is convinced that groundbreaking therapies of this nature offer significant opportunities for patients with this weakening of the heart muscle, a condition with one of the highest fatality rates worldwide. Considerable funding (worth 15 million euros) will now enable Cardior to develop its first new lead substance further, meaning that initial clinical data can be obtained in the near future.

"This spinoff company is highly visible proof that MHH is doing extremely well at translating knowledge from bench to bedside," comments the School's president Professor Christopher Baum.

### About Cardior Pharmaceuticals

Cardior's portfolio of patents have been licensed to the company by MHH, the Max-Planck Society and various French institutes. The firm won the Startup Challenge at the 2017 'Deutsche Biotechnologietage' event, and received initial assistance from Venture-Villa Inkubator GmbH, hannoverimpuls GmbH and Ascension. Cardior is pursuing translational approaches, has numerous academic and pharmaceutical collaborators both in Germany and worldwide, and is based on the MHH campus.



a researcher can test a new therapy for the treatment of lung diseases in animal models. Using quantitative microscopy, they can demonstrate that treatment is re-opening air spaces and (with a little luck) propose the molecular mechanism for the new drug by visualizing interaction with a key receptor. The teaching curriculum includes not only a comprehensive list of techniques (and the experts in the field they can be learned from), but also lectures on standardized image manipulation and ethics. Should the brightness and contrast of a western blot image be increased? TIFF or JPEG? Non-linear adjustment of images ... ? What is standard practice in scientific imaging processing? What is allowed by scientific journals? Training in image-

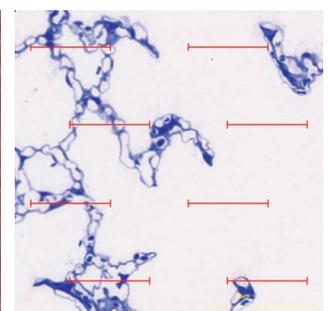
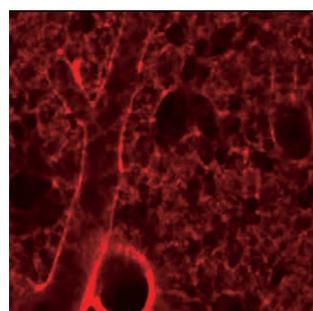
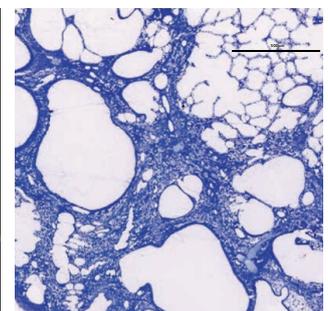
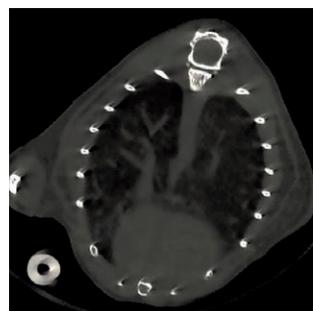
processing software is also part of the programme, so students can not only learn how to create images but also how to analyse and interpret them.

## Imaging in Biomedical Research

From *in vivo* non-invasive imaging of organs in animals to quantitative microscopic analysis *ex vivo* and molecular *in vitro* imaging: REBIRTH scientists from different imaging units have teamed up to train Hannover Medical School's (MHH) future researchers, offering a new optional module in the Master's in Biomedicine course. The 'Imaging in Biomedical Research' module gives Master's students the opportunity to learn the basics of different imaging techniques and applications in biomedical research. A team of researchers actively involved in biomedical research will teach students a battery of imaging techniques, available at MHH, to broaden their knowledge for their future research careers. "Seeing is believing" – well then, what can we see in biomedical research? With a CT (computed tomography) scan,

### Participating Units

- REBIRTH Unit Quantitative Microscopy in Regeneration
- REBIRTH Unit Small animal MRI
- MHH – Zentrale Forschungseinrichtung für Lasermikroskopie



# Alternatives to animal experimentation

'3R' is a threefold principle applied to animal testing. It involves finding alternative methods that replace these experiments, reducing the number of animals required, and refining these tests – by easing stress on the animals, for example. REBIRTH investigators are now addressing these aspects in a new research alliance: in 'R2N', scientists will

testing (usually on rats) is mandatory. "For as much as 99% of materials, we want to assess toxicity using a new, cell-based model and hence considerably lower the number of laboratory animals needed," says Professor Tobias Cantz (REBIRTH unit on Translational Hepatology and Stem Cell Biology) of Hannover Medical School's (MHH) Department of Gastroenterology, Hepatology and Endocrinology. To

this end, his team is devising a liver metabolism model from induced pluripotent stem cells (iPS cells) derived from the patient's own body. Employing the CRISPR/Cas method, individual genes can be modified to factor-in metabolic peculi-



be developing ways of replacing or complementing animal tests. "Our goal is to restrict the number of animals in experiments to the absolute minimum necessary," says REBIRTH member Professor André Bleich, Ph.D. The director of the Institute for Laboratory Animal Science and Central Animal Facility, he heads the new collaborative project that Lower Saxony's Ministry of Science and Culture is funding to the tune of 4.5 million euros as part of the way forward for biomedical research in the federal state.

One aim is to reduce animal experiments required by law for toxicity assays. At present, although a substance's toxicity is initially tested in cell culture, subsequent animal

arities that affect how drugs are processed in the body. Professor Cantz is involved in developing a miniature liver that, in conjunction with other organ models developed using micro-slides, is intended to reflect the way toxins are dealt with in the body as closely as possible. In the future, human-specific toxicity tests of this kind could be superior to animal experiments in both efficiency and reliability.

Also taking part in the R2N alliance are other REBIRTH work groups that are creating three-dimensional cell culture models as an alternative to animal testing. Professor Ulrich Martin (REBIRTH unit on iPSCs for Disease Modelling, Drug Screening and Cell Therapy) and Dr Ruth Olmer



(Leibniz Research Laboratories for Biotechnology and Artificial Organs, LEBAO), of MHH's Department of Cardiothoracic, Transplantation and Vascular Surgery (HTTG), are keen to use a model of this kind to test the effect and toxicity of substances on the lungs. Professor Bleich is studying bowel disease and potential remedies using an intestinal model.

Dr Andres Hilfiker (REBIRTH unit on Tissue Engineered Heart Valves) of LEBAO has devised an *in vitro* test to identify the antigens that need to be eliminated from decellularized pig heart valves in order to prevent a direct rejection reaction in patients following implantation. So that they can ascertain and assess the safety of gene therapy by means of sophisticated cell culture models and computer-assisted network analysis instead of animal experiments, Professor Axel Schambach and Dr Michael Rothe (REBIRTH unit on Regenerative Gene Therapy) of the Institute of Experimental Haematology are designing new procedures for verifying and predicting the safety of vectors in clinical gene therapy.

Work on developing these techniques is proceeding as rapidly as possible. If they are to be able to replace an animal experiment, however, they must be recognized by the approving authorities, which in the current situation may take another several years overall. The R2N team, which is also looking at this aspect, is therefore considering how the approval process can be speeded up and improved.

### The partners in this alliance:

The organizations behind the alliance are MHH, the University of Veterinary Medicine Hannover (TiHo), the University Medical Center Göttingen and the University of Hannover (LUH). Also involved are the TWINCORE Centre for Experimental and Clinical Infection Research, the Fraunhofer Institute of Toxicology and Experimental Medicine (ITEM) and the German Primate Centre (DPZ). Numerous investigators within REBIRTH are also participating in the project.

## REBIRTH scientist held in high regard

**Professor Illig is among the most frequently cited researchers Europe-wide in the field of molecular biology and genetics.**



Professor Thomas Illig, head of the central biobank and deputy director of Hannover Medical School's (MHH) Institute of Human Genetics, is one of the most often cited researchers Europe-wide within his

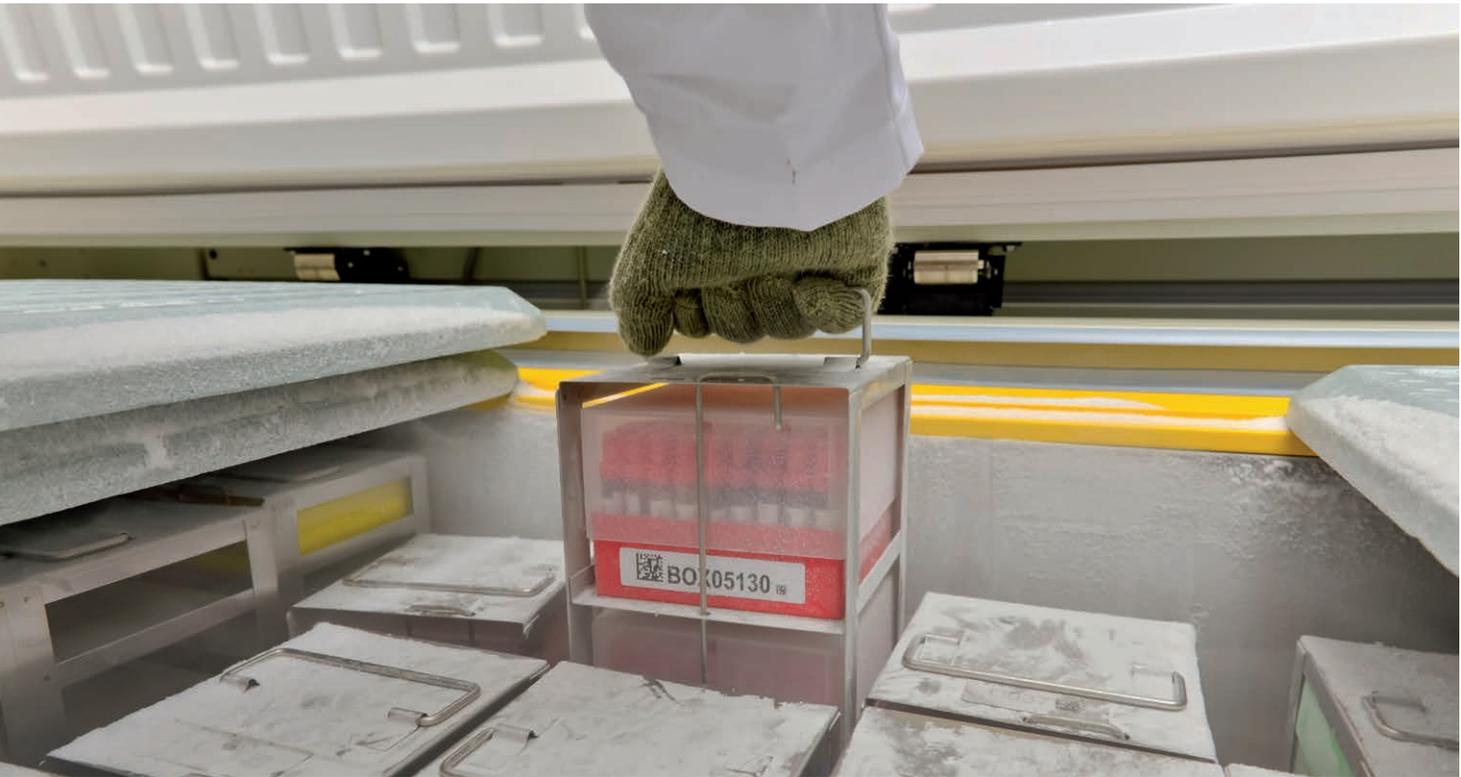
discipline, namely molecular biology and genetics. This was revealed by news magazine *Labtimes*. Its publication analysis is based on articles that appeared in journals between 2007 and 2013 which were cited by other researchers up until October 2016.

The *Labtimes* table, which drew on the Web of Science database by Thomson Reuters, lists the 30 most frequently cited investigators active in the area of molecular biology and genetics. REBIRTH member Professor Illig achieved 20th place.

His main research interest, alongside biobank research, is the interpretation of large-scale molecular-data sets ('omics' data) relating to cancer and rare diseases.

The list can be viewed online by following this link: [www.labtimes.org/labtimes/ranking/2016\\_06/index2.lasso](http://www.labtimes.org/labtimes/ranking/2016_06/index2.lasso)





*Storage of biosamples in the biobank*

## 14.4 million euros for integrating German biobanks

On 1 May 2017, German biobanks at 11 different locations joined forces to form the German Biobank Alliance (GBA). This paved the way for a national and Europe-wide scheme for exchanging biological samples and data between biobanks. The central biobank at Hannover Medical School (MHH), the Hannover Unified Biobank (HUB), is a partner in this network. "Germany's biobanks are committed to a pioneering shared initiative that is creating the foundation for a new generation of biobanks linked throughout Europe," explains Professor Fay Betsou, who chairs the initiative's scientific advisory board. The German Federal Ministry of Education and Research (BMBF) will be funding this alliance until 2020 to the tune of 14.4 million euros.

"Interconnected, state-of-the-art biobanks will be instrumental in developing innovative diagnostic techniques and treatments for patients," says REBIRTH member Professor Thomas Illig, director of HUB. Biobanks collect and store blood, tissue and other biomaterial, making this available for biomedical research. In this way, significant repositories of samples and data are built up for research on diseases. There are some 50 central biobanks in Germany.

Enabling biological materials and related data to be shared, both between German biobanks and within Europe, necessitates a large-scale process of harmonization. Not only must standards – governing the exchange of information and the quality of biosamples – be discussed and aligned, but ethical and legal aspects as well. Only in this way can biomaterial (and data on it) be amalgamated and used for research purposes in a manner that transcends individual biobanks and national borders.

[www.bbmri.de](http://www.bbmri.de)





*UniStem Day: Pupils in an operating theatre (left) and in a lab (right).*



## Out-of-school vocational education

What are stem cells, and how exactly can I become a scientist? On 17 March 2017, 25 pupils from selective secondary schools all over Lower Saxony, or attending Niedersächsisches Studienkolleg preparatory courses – all of them very interested in biology or medicine – attended the UniStem Day hosted by the REBIRTH Cluster of Excellence at Hannover Medical School (MHH). After an introductory session covering the basics and ethical aspects of stem cell biology, four REBIRTH units – one on each Cluster area: blood, heart, liver and lung – provided an inside look at the labs and their research. Here, pupils practised pipetting and microscopy, and asked a great many questions. A small group of medically-minded youngsters were shown an operating theatre at the Department of Cardiothoracic,

Transplantation and Vascular Surgery. In a Meet the Expert discussion, the youngsters were able to talk face-to-face with medical lab scientists, undergraduates and Ph.D. students about personal career choices.

The UniStem Day was held in 10 German cities. Up and down the country, more than 1,000 upper-school pupils visited research institutions to explore stem cells, research into them and their application. The idea behind it is a European-level one: for more than 27,000 young people in Italy, Spain, Sweden, Poland, Serbia, Denmark and Germany, 17 March was a special day for finding out about these cells so fundamental to life. Talks, games, ethical debates, lab tours, panel discussions and meetings with experts raised pupils' awareness of many aspects of current research – both basic investigations and potential medical uses – as well as career opportunities.

# Funding for personalized medicine

In a call for proposals entitled 'Funding Initiative for Innovative Stem Cell Technologies in Personalized Medicine', Germany's Federal Ministry of Education and Research (BMBF) is funding not one but two projects within the REBIRTH Cluster of Excellence for three years: **iCARE and i-MAC.**

## iCARE

Heart disease caused by insufficient blood supply to this organ is the number-one cause of death worldwide, with 7.4 million fatalities every year. Although various therapeutic approaches are available, in many cases the 'last resort' of a heart transplant is the only option. In this collaborative project iCare (induced pluripotent stem cells for Clinically Applicable heart Repair), launched on 1 April 2017 and funded for three years to the tune of more than three million euros, a group of scientists headed by coordinator Professor Ulrich Martin, REBIRTH Unit iPSCs for Disease Modelling, Drug Screening and Cell Therapy and head of Leibniz Research Laboratories for Biotechnology and Artificial Organs (LEBAO), will be investigating potential therapeutic applications involving cardiac muscle cells derived from induced pluripotent stem cells (iPS cells). The partners in this alliance are aiming to develop the world's first clinical application for cardiac therapy using iPS cells. "Our consortium is one of the few worldwide that combines the necessary expertise with the technology needed to move iPS cell-based therapies for heart disease into the clinic," says Professor Ulrich Martin, deputy coordinator of the REBIRTH Cluster of Excellence.

Over the three-year period, this will involve the researchers



*Upscaling: production of cardiac muscle cells derived from iPS cells in a bioreactor.*



*Characterization of heart tissue derived from iPS cells in a bioreactor.*

generating genetically enriched cardiac muscle cells produced from human iPS (hiPS) cells, which they will study in a preclinical heart therapy model. To facilitate clinical application, the partners devised quality-assurance proto-



cols in line with good manufacturing practice (GMP), both for the reprogramming process and the genetic modification of iPS cells. For the scientists, large-scale cell production is just as important a goal as the enrichment of different iPS cell-derived cardiac muscle types and in-depth characterization of the engineered cells. The alliance is also addressing the development of the regulatory framework governing intramyocardial transplantation of generated cardiac muscle cells into patients, and seeking to clarify ethical and legal issues

## Participating partners:

- MHH-Department of Cardiothoracic, Transplantation and Vascular Surgery (HTTG)
- MHH-Institute of Cellular Therapeutics (IZT)
- Fraunhofer Institute of Toxicology and Experimental Medicine, Hannover (ITEM)
- German Primate Center (DPZ)
- Centre for Ethics and Law in the Life Sciences (CELLS) at the University of Hannover (LUH)
- Miltenyi Biotec GmbH
- corlife oHG



*Aseptic cell processing in a Class A environment in accordance with EU GMP guidelines.*

## i-MAC

Scientists on the i-MAC collaborative project are investigating whether gene-corrected macrophages derived from induced pluripotent stem cells (iPS cells) – known as i-MACs – constitute a safe and effective source for use in

modern cellular and gene therapy. This approach is being explored for two model diseases, hereditary pulmonary alveolar proteinosis (PAP) and chronic granulomatous disease-associated colitis (CGD-col). The project, launched on 1 March 2017, is to receive just under 2.3 million euros in funding and will be coordinated by Professor Thomas Moritz (REBIRTH Unit iPSC based Haematopoietic Regeneration, MHH). Its work programme is divided into five subprojects, three to be carried out at MHH and two at Frankfurt University Hospital (UKF). The partners have already succeeded in demonstrating the generation of gene-corrected functional i-MACs for both target diseases. The consortium now aims to establish GMP-compliant, quality-assured methods for producing patient-specific iPS cell lines, their genetic repair by means of state-of-the-art designer nuclease technology, and their expansion and differentiation into fully functional macrophages for therapeutic use.

Both PAP and CGD-col are rare diseases in which the immune system's scavenger cells (macrophages) are compromised or defective. The first step in this new therapeutic approach involves producing healthy macrophage progenitors in cell culture from induced pluripotent stem cells. These cells are then transplanted directly into the relevant organ, where they mature into functional macrophages and do the job of the defective cells. However, before the cells can be transplanted into the body, the scientists first correct – in cell culture – the gene defect responsible for the condition. Designer nucleases are employed for this purpose.

## Participating partners:

- MHH-Institute of Experimental Haematology
- MHH-LEBAO, HTTG
- MHH-Department of Paediatric Pulmonology, Allergology and Neonatology
- MHH-Institute of Cellular Therapeutics (IZT)
- University Medical Center Freiburg (UKF)



PD Dr. Ina Gruh and Dr. Markus Döring from the Flad & Flad agency, which has designed the InnoTruck, are looking at the displays.



## Innovation ambassadors: REBIRTH on an important mission

On 24 April 2017, at the Hannover Messe trade show, Germany's federal minister for education and science Professor Johanna Wanka unveiled her ministry's new information and dialogue initiative: the two-level 'InnoTruck'. Inside the vehicle is an exhibition, including more than 80 informative exhibits, which showcases the key challenges of the future under the new High-Tech Strategy, as well as related areas of technology. On board are bioreactors for growing cardiac muscle cells and tissue, as well as both a decellularized and a mechanical heart valve. The idea is that these displays from various REBIRTH work groups will, under the heading of 'Healthy Living', illustrate research



into regenerative medicine in Germany with reference to the heart.

“I’m delighted that we’ve been selected to present our research to a wide audience,” says Dr Ina Gruh. She heads the REBIRTH unit on Myocardial Tissue Engineering, which oversaw the development of REBIRTH’s exhibits. “For school pupils, the InnoTruck has a wealth of fascinating things to discover, some of which aren’t on the curriculum and are well worth exploring – they might even end up going into research themselves!”

The InnoTruck will be on tour until 2020, visiting up to 80 different places a year throughout Germany and spotlighting the role of innovation in our everyday lives.

As the exhibits are aimed equally at youngsters and adults, this stimulating mobile experience will make stops at schools, trade fairs and exhibitions, technology events, town fairs and many other public venues.

[www.innotruck.de](http://www.innotruck.de)



# Performance Center Translational Medical Engineering opens

On 25 April 2017, Lower Saxony's minister for science and culture Dr Gabriele Heinen-Kljajić and Professor Reimund Neugebauer, president of the Fraunhofer-Gesellschaft,



*Representatives have opened the High-Performance Center Translational Medical Engineering (from left to right): Dr Gabriele Heinen-Kljajić, Lower Saxony's minister for science and culture; Professor Theodor Doll, head of the High-Performance Center; Professor Norbert Krug, director of Fraunhofer ITEM; Professor Reimund Neugebauer, president of the Fraunhofer-Gesellschaft; Professor Christopher Baum, president of MHH; and Thomas Lenarz, professor and chairman of MHH's Department of Otorhinolaryngology (sitting at the front).*

opened Hannover's new High-Performance Center Translational Medical Engineering. They were joined by representatives from industry, government and academia.

The new Center is aimed at bringing medical devices from the lab into phase I of clinical development. Its focus is on active implants – i.e. electrical stimulation systems such as cochlear and retinal implants – and technological solutions for inhaled drug delivery. The latter are being systematically developed with smart drug/device combination products in mind. The Center is funded by the Lower Saxony government and the Fraunhofer-Gesellschaft. “Be it research on and development of implants, regenerative or personalized medicine – we want this facility in Hannover to contribute to overcoming the difficult step of transferring medical research findings into clinical application, so that patients can benefit from novel products and methods. The new High-Performance Center Translational Biomedical Engineering provides a valuable link between research institutions and industry. It further strengthens the close network of research in the life sciences in Hannover,” said Dr Heinen-Kljajić. Professor Theodor Doll, head of the facility, also spoke about the new Center.

“Here we will assist researchers, companies and entrepreneurs from the development phase onwards. Dedicated manufacturing processes, for example, commonly represent substantial economic hurdles for small and medium-sized enterprises. Furthermore, medical devices equally have to go through quality-assurance and risk assessment processes before they can progress to clinical trials. We navigate the sophisticated processes of bringing devices from basic research to clinical application – we help get them through the ‘translation bottleneck’, so to speak.” Doll holds a professorship instituted at Hannover Medical School (MHH) in collaboration with Fraunhofer ITEM. It directly connects the research done in the REBIRTH and Hearing4all Clusters of Excellence in Hannover, and in the Lower Saxony consortium Biofabrication for NIFE, with the translation expertise of Fraunhofer ITEM.

[www.item.fraunhofer.de/de/leistungszentrum-translazionale-medizintechnik.html](http://www.item.fraunhofer.de/de/leistungszentrum-translazionale-medizintechnik.html)





## FUNDING: Scar tissue in the liver can be revitalized

Numerous medical conditions could be remedied if we could take diseased cells – from the liver of cirrhosis sufferers, for instance – and transform them into healthy ones *in situ* in the body. Researchers belonging to the REBIRTH unit on miRNA in Liver Regeneration at Hannover Medical School (MHH) are getting closer to this aim. A year ago they succeeded, aided by four genetic factors and inactivated adenoviruses, in changing liver scar tissue into



Dr Amar Deep Sharma at his microscope.

healthy, functioning tissue, and in diminishing the scarring process. Although this was observed in mice, Dr Amar Deep Sharma of MHH's Department of Gastroenterology, Hepatology and Endocrinology is looking to apply this approach to achieve long-term benefits in people. He is now seeking to transform scars in the human liver – those of cirrhosis patients, for example – into healthy liver cells, both *in vitro* and (in mice) *in vivo*. Boehringer Ingelheim Fonds is funding his project to the tune of 900,000 euros over three years. "Dr Sharma's work is opening up new avenues to treating not just liver disease, but also scar processes affecting other organs that may result from chronic inflammation," says Professor Michael Manns, director of MHH's Department of Gastroenterology, Hepatology and Endocrinology

## News from the Ph.D. programme

This year's retreat for students at all stages of the Ph.D. programme in Regenerative Sciences was held at the tried-and-tested TWINCORE venue on 2 and 3 May 2017. The newest students (2016 intake) presented their projects by means of posters. Those in their second or third year gave a talk about their research findings as they currently stand. As usual, prizes were given for the best presentations in each category. As of 2016, one such honour is awarded by the group leaders present, and another by the Ph.D. students themselves. The poster awards went to Ewa Janosz of the REBIRTH unit on iPS-based Haematopoietic Stem Cells (Department of Experimental Haematology) and Lika Drakhlis of the REBIRTH unit on Mass Production of Pluripotent Stem Cells and Derivates (Leibniz Research Laboratories for Biotechnology and Artificial Organs, LBAO). This year's prizes for best oral presentation went to Shambhabi Chatterjee (of Christian Bär's work group at the Institute of Molecular and Translational Therapy Strategies, IMTTS) and Denise Klatt of the REBIRTH unit on Regenerative Gene Therapy (Department of Experimental Haematology). All Ph.D. students who started in 2015 received a certificate for passing their intermediate exams in March.

Also in March, Kathrin Haake, one of the two year representatives in 2016, was elected as deputy doctoral representative on Hannover Medical School's (MHH) Senate. This is the first time that doctoral students have been invited onto the School's supreme academic body, which is elected every two years.



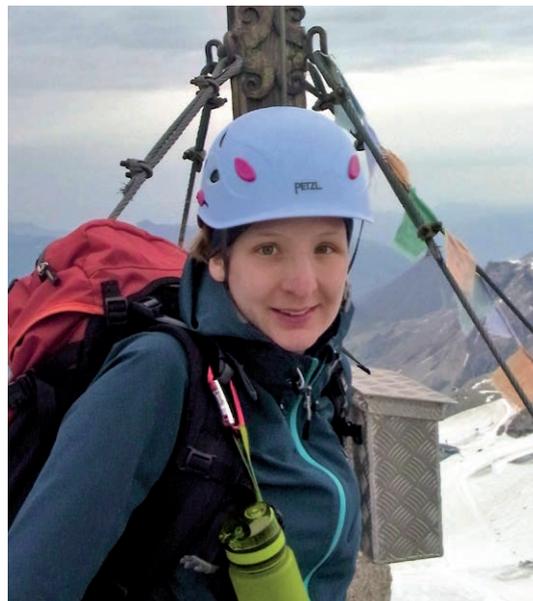
Kathrin Haake,  
new MHH Senate representative

### What are you working on and why?

My Ph.D. project is all about the use of designer nucleases, specifically CRISPR-Cas9 systems, as a tool for correcting monogenic disorders and generating disease models. My focus is on a primary immunodeficiency called chronic granulomatous disease. This condition involves a defect in NADPH oxidase, a complex that plays a key role in the production of reactive oxygen species and in pathogen control. We want to use the CRISPR-Cas9 system to develop novel approaches to the treatment of this disease, and to further unravel the mechanisms involved in its pathogenesis.

### Why did you decide to enrol in the Ph.D. programme in Regenerative Sciences?

I opted for the Ph.D. programme in Regenerative Sciences at Hannover Medical School (MHH) as the REBIRTH Cluster of Excellence's focus on these four organ systems (heart, lung, liver and blood) and the Ph.D. curriculum were a good match with my interests. And there are many other plus sides to this programme. This includes the networking aspect and the interdisciplinary nature of REBIRTH, getting to know other doctoral students from different countries, and the wide range of skills-upgrading courses on offer. I also really enjoy the annual Ph.D. retreat, as this gives us the opportunity to discuss our projects in greater depth.



## PhD Programm Regenerative Sciences

# Who is Who

**Denise Klatt** (26) from Germany,  
REBIRTH Unit 6.2 –  
Regenerative Gene Therapy

### What do you like about your doctoral thesis?

Although doing a Ph.D. can often be a stressful time, I particularly appreciate gradually gaining scientific independence. Especially during the first two years, you have the time to devise experiments yourself, learn new methods and perhaps develop the first side project of your own. I also really enjoy collaborating on a project with colleagues or other group members. That way you not only have your perspective broadened and learn new things, but make your first contacts with other researchers.

### What do you do in your spare time?

Several years ago I fell in love with the Alps. If possible, I spend one or two weeks there every summer – hiking, climbing and conquering summits. Most of all I like spending time off the beaten track, where I can enjoy the beauty of the mountains undisturbed. This summer I'm headed for Switzerland, where I aim to climb my first 4,000-metre peak.

### What three things would you take to a desert island?

Assuming it was an island in the South Pacific, I'd take the following three things with me: a pipette, a microscope and some slides. What for? To catch my first *Trichoplax adhaerens* specimen – a multicellular animal that is the only living species in its phylum! More realistically, I'd probably take a charged satellite phone, a Bear Grylls-style survival knife and a desalinator for generating drinking water.