rebirth news 4 DECEMBER 2016

COVER STORY

Development of the lung: researchers identify key regulatory pathway

RESEARCH
Protein promotes abnormal heart growth

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Latest Publications

MicroRNAs in nanoparticles

Blood vessels are internally lined with a protective cell layer, the endothelium. Over the course of a lifetime this layer wears away, and the vascular walls thicken and calcify. These changes are often the cause of medical conditions such as myocardial infarction or stroke. In this research, the investigators developed a new therapy aiding the recovery of vessels damaged in this way. The key aspect was the introduction of microRNA 126 into damaged vessels by means of tiny, degradable lipid nanoparticles. Due to the presence of this microRNA, the cells in the damaged vascular wall regenerated themselves much more rapidly, and the vessel was successfully repaired. The scientists demonstrated this both in experiments with a mouse model and also using human tissue samples.

Publication

Hartmann D, Fiedler J, Sonnenschein K, Just A, Pfanne A, Zimmer K, Remke J, Foinquinos A, Butzlaff M, Schimmel K, Maegdefessel L, Hilfiker-Kleiner D, Lachmann N, Schober A, Froese N, Heineke J, Bauersachs J, Batkai S, Thum T. MicroRNArna-Based Therapy of Gata2-Deficient Vascular Disease. *Circulation*. 2016;25(116):022478. Epub 2016/10/27.

Model for diseases of the cardiac muscle

Heart muscle cells (cardiomyocytes) derived from human embryonic stem cells (hESC-CMs) have considerable potential for *in vitro* models of cardiac muscle diseases. Researchers had not previously succeeded in growing hESC-CMs that, as with ventricular human cardiomyocytes, express only β-cardiac myosin. Comparison of protein expression and contractile properties in two *in vitro* cultivation models enabled the investigators to show that culture on a stiff matrix allows generation of hESC-CMs which solely express β-cardiac myosin, making them suitable for *in vitro* analysis of cardiomyopathies and drug screening.

Publication

Stiff matrix induces switch to pure β-cardiac myosin heavy chain expression in human ESC-derived cardiomyocytes. Weber N, Schwanke K, Greten S, Wendland M, Iorga B, Fischer M, Geers-Knörr C, Hegermann J, Wrede C, Fiedler J, Kempf H, Franke A, Piep B, Pfanne A, Thum T, Martin U, Brenner B, Zweigerdt R, Kraft T. *Basic Res Cardiol*. 2016 Nov;111(6):68.

Natural spermidine protects the heart

In this publication, researchers showed that administration of spermidine, a natural polyamine, extends the life of mice and has protective effects for the heart resulting in reduction of hypertrophy and in maintenance of diastolic function in aged mice. The team led by Professor Mühlfeld carried out the morphological and stereological investigations involved in this work.

Publication

Eisenberg T, Abdellatif M, Schroeder S, Primessnig U, Stekovic S, Pendl T, Harger A, Schipke J, Zimmermann A, Schmidt A, Tong M, Ruckenstuhl C, Dammbrueck C, Gross AS, Herbst V, Magnes C, Trausinger G, Narath S, Meinitzer A, Hu Z, Kirsch A, Eller K, Carmona-Gutierrez D, Buttner S, Pietrocola F, Knittelfelder O, Schrepfer E, Rockenfeller P, Simonini C, Rahn A, Horsch M, Moreth K, Beckers J, Fuchs H, Gailus-Durner V, Neff F, Janik D, Rathkolb B, Rozman JA-Ohoo, de Angelis MHA-Ohoo, Moustafa T, Haemmerle G, Mayr MA-OhooX, Willeit P, von Frieling-Salewsky M, Pieske B, Scorrano LA-Ohoo, Pieber T, Pechlaner R, Willeit JA-Ohoo, Sigrist SJ, Linke WAA-Ohoo, Muhlfeld C, Sadoshima J, Dengjel J, Kiechl S, Kroemer G, Sedej SA-Ohoo, Madeo F. Cardioprotection and Lifespan Extension by the Natural Polyamine Spermidine. Lid - 10.1038/Nm.4222 [Doi]. *Nat Med*. 2016

Biomarker for vascular diseases

Changes in the coronary arteries (cardiac allograft vasculopathy) are the main cause of illness and death following a heart transplant. Thus far, it has been possible to diagnose these diseases only by means of coronary angiography; a non-invasive diagnostic biomarker has not yet been found. This study's investigators identified microRNA miR-628-5p as a novel potential biomarker – detectable in the blood – for this condition.

Publication

MicroRNA 628-5p as a novel biomarker for cardiac allograft vasculopathy. Neumann A, Napp LC, Kleeberger JA, Benecke N, Pfanne A, Haverich A, Thum T, Bara C. *Transplantation*. 2016 Sep 21.

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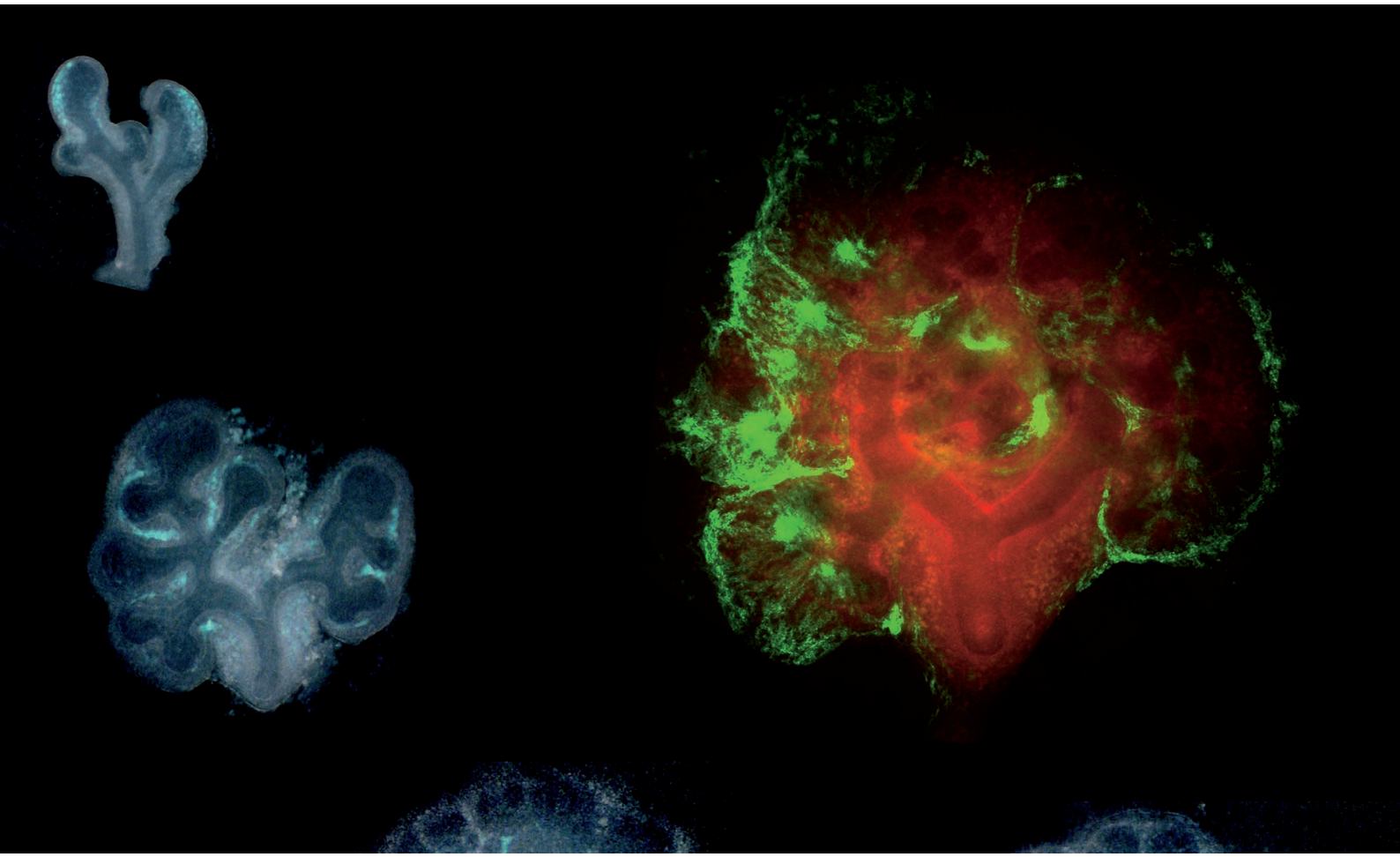

The three germ layers

During embryonic development in the uterus, the third week sees the first specialization of the mass of cells, resulting in three germ layers; the endodern, mesodern and ectoderm. Each of these germ layers subsequently develops into specific tissues and organs. For example, the endoderm gives rise to (among other structures) the digestive tract, the liver and the respiratory tract.

Pharmacological treatments of lung organ cultures to unravel the interconnection of Tbx2- and Tbx3- dependent developmental signaling pathways in the lung. The image shows an autofluorescent photograph of the tissue-specific activation of a green fluorescent reporter in lung rudiments ($Wt1^{creERT2/+}$;$Rosa26^{mTmG/+}$) on day 11.5 and the inverted brightfield images of a lung culture timeline that was used to evaluate organ growth and branching morphogenesis.

Dr Timo Lüdtke, the study's lead author (left), and Professor Andreas Kispert at the incubator with a culture tray for embryonic primordia.

Development of the lung: researchers identify key regulatory pathway

How does the branching structure of the airways form during embryonic development?

The main function of the human lung is that of gas exchange between the blood and the air. In order that this exchange occurs efficiently, the air is carried by a highly branched conduction system, the bronchial tree, to clusters of tiny sacs called the alveoli, in which close contact with the vascular system takes place over a large surface area. During embryonic development, the bronchial tree and its alveoli form from a simple protusion of the foregut – part of the endoderm. This involves a single bud with a single-layered cell complex, an epithelium, growing into the loose connective tissue (mesenchyme) that surrounds it, and branching into a treelike structure by regular division of the bud tip. Earlier studies had already shown that this growth requires a continuous exchange of signals between the epithelium and the mesenchyme. Researchers at Hannover Medical School (MHH) have now discovered an im-

portant molecular switch that controls the signal-mediated communication between epithelium and mesenchyme at the buds during the growth of the bronchial system in embryonic development.

The team, led by Professor Andreas Kispert and Dr Timo Lüdtke of the REBIRTH unit on Transcriptional Control of Organogenesis, found out that two closely related transcription factors, Tbx2 and Tbx3, are activated by signals from the lung bud in mesenchyme that surrounds this bud. Here, they ensure that the lungs grow and that the bronchial tree branches during embryonic development. The scientists elucidated how this works by means of experiments – using a mouse model and culture systems – with primordial lungs in mouse embryos. They describe the precise mechanism in the latest issue of the prestigious journal *Developmental Cell*. "Our findings could, in the long term, help patients with pulmonary conditions such as idiopathic fibrosis," says Professor Kispert. "In this disease, these embryonic signalling pathways and Tbx2 are reactivated and there is an increase in the formation of connective-tissue cells that give these patients difficulties in breathing." Dr Lüdtke adds: "In cases of lung cancer, too, it has recently become known that Tbx2 can be reactivated, making the tumour more agressive. Knowledge about the effect of this key embryonic factor may help to understand and treat cancer better."

The signalling pathway that the researchers unravelled

Tbx2 and Tbx3 are transcription factors that coordinate the activity of two important signalling pathways during lung development. In embryonic primordial lungs, these factors mediate communication between the Sonic Hedgehog signalling pathway in the epithelial part of the lung bud and the Wnt signalling pathweg in the surrounding mesenchyme. They do this by locally preventing the transcription of certain genes. Among them are factors that inhibit the Wnt signalling pathway and the genes for p21/27, which interrupt cell proliferation. Both mechanisms ensure intensive lung growth in the embryo. Mice in which these transcription factors occur at lower levels, or not at all, develop only very small lungs as a result.

Publication:
Lüdtke TH, Rudat C, Wojahn I, Weiss AC, Kleppa MJ, Kurz J, Farin HF, Moon A, Christoffels VM, Kispert A. Tbx2 and Tbx3 Act Downstream of Shh to Maintain Canonical Wnt Signaling During Branching Morphogenesis of the Murine Lung. Dev Cell. *2016;39(2):239-53. Epub 2016/10/26.*

About this publication

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From right: Professor Thomas Thum and Shashi K. Gupta in the lab.

Age-adjusted therapy for heart attack patients

Inhibition of microRNA 22 has positive effects for elderly patients with myocardial infarction.

Researchers at Hannover Medical School (MHH) have taken strides towards a new therapy for myocardial infarction (heart attack) that is especially suitable for elderly patients. The team led by Professor Thomas Thum and Shashi K. Gupta, from MHH's Institute of Molecular and Translational Therapeutic Strategies (IMTTS), discovered two positive effects resulting from inhibition of a particular ribonucleic acid chain (microRNA 22). Firstly, it stops abnormal heart growth and thus prevents cardiac insufficiency, and secondly, it facilitates cellular 'rubbish disposal' by promoting the breakdown and removal of waste products. The scientists demonstrated this in cellular and mouse experiments.

"These effects are particularly evident in older mice, as they have a lot more microRNA 22 in the heart tissue than younger mice do," says Professor Thum. The investigators found this age-dependent distribution of microRNA 22 in human cardiac muscle tissue as well. This paves the way for age-adjusted therapy for heart attack patients. The aim is to enhance this therapy until it can be used on patients. They researchers published their findings in the *Journal of the American College of Cardiology*.

MicroRNAs are short ribonucleic acid chains. They generally influence an entire network of genes, by means of which they control the development, proliferation and function of cells.

The IMTTS is incorporated into the Integrated Research and Treatment Centre Transplantation (IFB-Tx) and into the REBIRTH Cluster of Excellence.

Publication:
Gupta SK, Foinquinos A, Thum S, Remke J, Zimmer K, Bauters C, de Groote P, Boon RA, de Windt LJ, Preissl S, Hein L, Batkai S, Pinet F, Thum T. Preclinical Development of a Microrna-Based Therapy for Elderly Patients with Myocardial Infarction. J Am Coll Cardiol. *2016;68(14):1557-71. Epub 2016/10/01.*

An **interview** on this publication with Professor Thum and Professor Axel Haverich, coordinator of the Cluster of Excellence, is available. Just follow this link: http://www.rebirth-hannover.de/index.php?id=250.

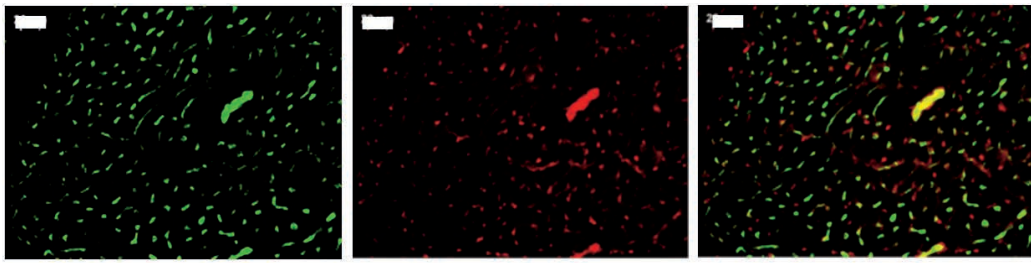
Protein promotes abnormal heart growth

REBIRTH researchers discovered that inhibition of a protein may be able to prevent cardiac sufficiency and heart failure.

Researchers have succeeded in stopping abnormal heart growth (cardiac hypertrophy) by inhibiting a protein called CTRP9. This was achieved by the team led by Professor Jörg Heineke, working with a mouse model and cardiac muscle cells. The scientists from the REBIRTH unit on Myocardial Cellular Crosstalk and Gene Therapy published their findings in the journal *Circulation Research*. The lead authors are Dr Mahesh Appari and Dr Astrid Breitbart.

Pathological heart growth resulting in cardiac insufficiency and even heart failure may result from elevated blood pressure over a period of years. "Levels of CTRP9 in chronically enlarged hearts are 20 times as high as in healthy heart muscle," explains Professor Heineke. His team found out that this protein originates from the blood vessels of the heart and stimulates abnormal growth of the cardiac muscle cells. Mouse hearts lacking this protein do not grow as much, and lay down less connective tissue; they work better and do not weaken. By contrast, mouse hearts with a lot of CTRP9 show increased growth and are rapidly prone to cardiac insufficiency.

IsolectinB4 (green) labels the endothelial cells, anti-beta galactosidase (red) the CTRP9-expressing cells. The overlay (merge) shows that CTRP9 originates from the endothelial cells of the heart.



Isolectin B4 | Anti-β-Galactosidase | Merge

Professor Heineke sums up the findings as follows: "With regard to slowly progressing chronic cardiac hypertrophy, deactivating CTRP9 could be beneficial – possibly involving an antibody therapy." His work group has also managed to unravel the underlying mechanism: the protein affects certain signalling pathways in the cardiac muscle cells, with two signal proteins - ERK5 and GATA4 – playing a key role.

Professor Jörg Heineke opening an incubator in which cardiac muscle cells and endothelial cells are being grown

Publication:
Appari M, Breitbart A, Brandes F, Szaroszyk M, Froese N, Korf-Klingebiel M, Malek Mohammadi M, Grund A, Scharf GM, Wang H, Zwadlo C, Fraccarollo D, Schrameck U, Nemer M, Wong W, Katus HA, Wollert KC, Muller OJ, Bauersachs J, Heineke J. C1q-Tnf-Related Protein-9 Promotes Cardiac Hypertrophy and Failure. Circ Res. *2016. Epub 2016/11/09.*

Cardiac replacement tissue from the stomach's mucosal lining

A new way of replacing tissue damaged by a heart attack?

Dr Felix Fleißner, a junior doctor (*Assistenzarzt*) at the Department of Cardiothoracic, Transplantation and Vascular Surgery (HTTG), is currently specializing as a heart surgeon. While in the 'rotating' research post ('Gerok position') that he holds, he developed experiments on large animals in which he tested the mucosal lining from the stomach as a cardiac replacement tissue. "We have, in the past, already successfully used the duodenum as a replacement for the right atrium both in animal experimental studies and, in individual cases, clinically in humans," says Dr Fleißner. "However, the higher pressure in the left heart means that this tissue is unsuitable in terms of its properties, so that gastric mucosa appears far more suitable for use here."

He prepared the mucosa for the operation of large animals such that its blood supply was preserved. This is referred to as a pedicled patch, and it was put in place by Dr Fleißner under the supervision of HTTG senior physician Dr Serghei Cebotari (of the REBIRTH unit on Large Animal Models for Myocardial Repair) in an open-heart procedure to replace left-ventricular cardiac tissue. He additionally removed progenitor cells from the atrial auricle, which he then introduced into the patch in order to achieve their differentiation into cardiac muscle cells and thus ensure the patch graft's contractility. As with humans, he connected the animals up to a heart-lung machine and artificially lowered their body temperature so as to reduce both metabolic and heart rate. This provides better protection for the animals' hearts and brains during and after the operation. "Despite the complexity of the surgery, with a long period on the heart-lung machine and lengthy aftercare, the survival rate (mortality and morbidity) achieved was acceptable. Overall, this approach seems highly promising, although more experiments are required here to ensure further standardization," Dr Fleißner adds.

Rotating posts for doctors

Researchers in the medical field tend to have a great deal of their capacity taken up with healthcare provision. Under a project funded by the German Research Foundation (DFG), an opportunity has therefore been created to hold a special 'rotating' post. Physicians already working in a given research establishment – and whose duties chiefly consist of patient care – can be temporarily given time off from their clinical obligations. During this period, they can devote themselves entirely to a scientific project and upgrade their skills in research.

Joining forces to find replacements for organs

Unique research alliance 'Biology of xenogenous cell' and organ transplantation – from bench to bedside' to be extended.

Demand for donor organs far outstrips the supply. This means that patients often wait several years for a transplant, and many of them do not survive this period: in Germany, an average of three patients on the waiting list die every day. In most instances, organ replacement solutions such as dialysis or an artifical heart can generally replace organ function only temporarily, and it is not yet possible to grow replacement organs from stem cells. Xenotransplantation – in this case, transplanting organs and tissues from pigs into humans – may well be a promising alternative. These issues are being addressed by a globally unique research alliance called 'Biology of xenogenous cell and organ transplantation – from bench to bedside'. This Collaborative Research Centre (SFB) / Transregio 127, with locations in Hannover, Munich and Dresden, is now to receive around 15 million euros in further funding from the German Research Foundation (DFG) over the next four years. Of this, Hannover Medical School (MHH) will obtain about 2.3 million euros. Among those participating in this project, which emerged from the DFG-funded research group on xenotransplantation, are scientists from four REBIRTH units: those on Tolerogenic Cell Therapy, Tissue Engineered Heart Valves, Large Animal Models, and Ethical and Legal Dimensions.

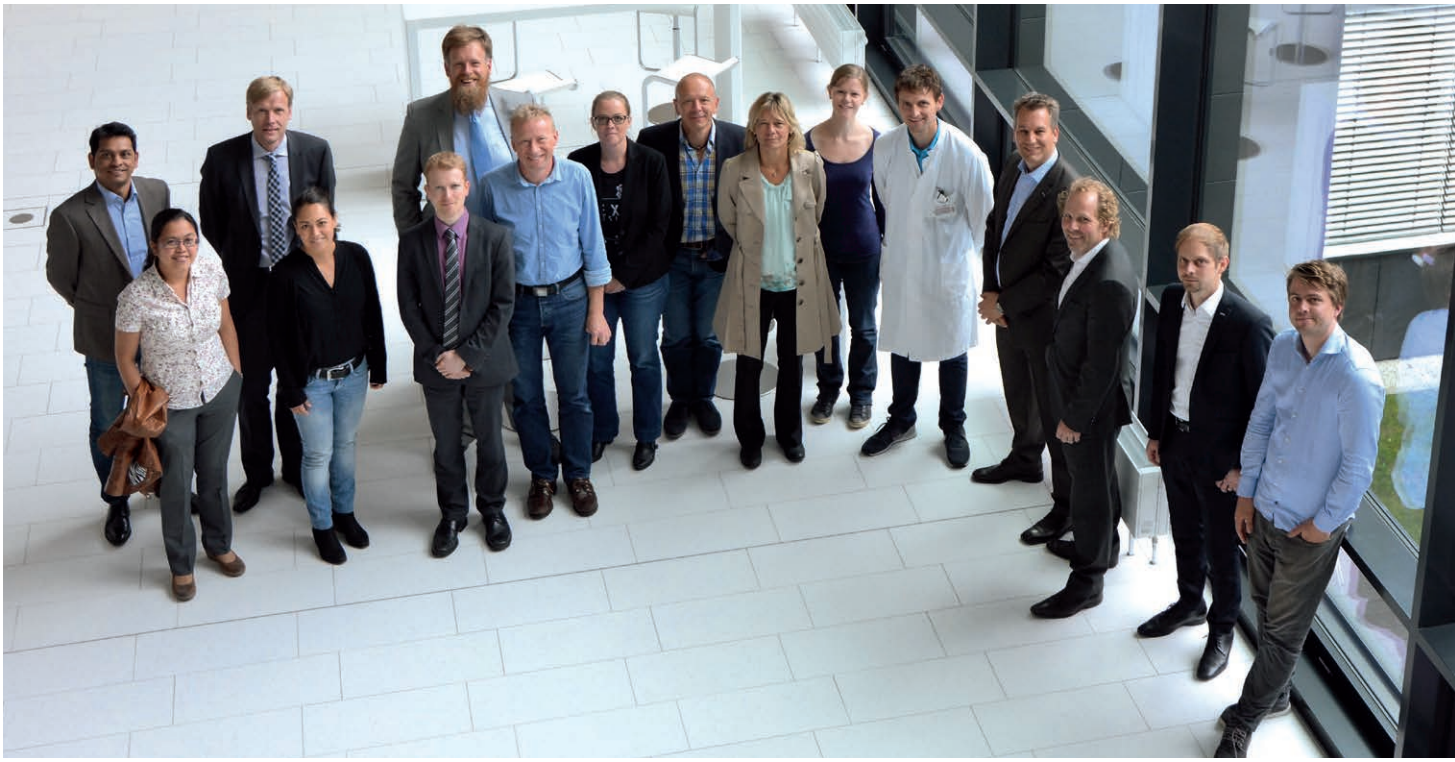
During the new funding period, the aim is that we will see the first transplants of insulin-producing cells and heart valves in humans. Other (long-term) goals include the transplantation of solid organs such as the heart. To this end, the researchers will be investigating the immue response to the transplanted organ or tissue. To prevent rejection by the patient, cells and organs derived from pigs will be genetically modified enabling them to be used as transplants in people.

In order to prevent the transmission to humans of infection pathogens found in pigs, research teams at the Robert Koch Institute and the Paul Ehrlich Institute are involved in this research consortium. Ethicists and medical legal professionals are also participating in this project, as the use of tissue and organs of animal origin is associated with new ethical and legal challenges.

Participating partners

- Hannover Medical School (MHH)
- Friedrich Loeffler Institute's (FLI) Institute of Farm Animal Genetics in Neustadt-Mariensee
- Leibniz University of Hannover (LUH)
- German Primate Center (DPZ) in Göttingen
- Ludwig-Maximilians-Universität München (LMU) (coordinating university)
- Technische Universität Dresden (TUD)
- Technical University of Munich (TUM)
- Helmholtz Zentrum München
- Robert Koch Institute (RKI)
- Paul Ehrlich Institute (PEI)

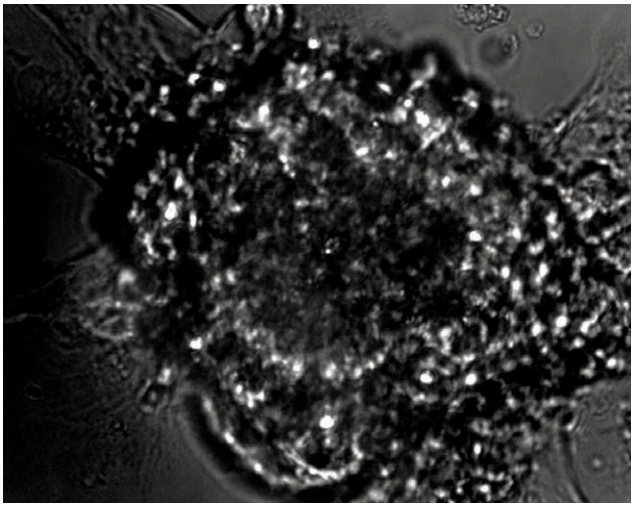
The project team at its kick-off meeting in NIFE



Optical cardiac pacemaker: a light-hearted approach

The goal: Cardiac arrhythmia can be treated more gently by specific stimulation of the heart muscle and other muscle groups – using light.

In the collaborative project called 'Biohybrids for Photon-Activated Cardiac Excitation' (BioPACE), funded by the German Federal Ministry of Education and Research (BMBF) to the tune of two million euros over three years, REBIRTH researchers at research centre Laser Zentrum Hannover e. V. (LZH) and Hannover Medical School (MHH) are – in conjunction with three other partners – developing a biohybrid pacemaker. Whereas conventional cardiac pacemakers stimulate the heart by means of electrical impulses, the aim with this new procedure is to use optical impulses. The heart muscle will be made to contract not by electrical stimulation but by applying light.



Interdisciplinary collaboration

The new pacemaker is to consist partly of biological material. To this end, REBIRTH scientists led by Dr Robert Zweigerdt and Dr Ina Gruh are producing modified and reprogrammed cells, derived from the patient him- or herself, and using these to develop cardiac muscle constructs that respond to optical stimulation. To achieve efficient stimu-

A cluster of cardiac muscle cells onto which a circular pattern of dots is projected. This optical stimulation causes them to contract. The contraction rhythm is controlled by the frequency of projection.

lation even deep within the construct, the REBIRTH team headed by Professor Alexander Heisterkamp is introducing what are known as upconverting nanoparticles (UCNPs). If these nanoparticles are optically stimulated, they convert the excitation light into radiation with other wavelengths that, by means of photoswitchable molecules called channelrhodopsins, triggers contraction of the cells. The impulse is imparted to the surrounding cells, causing the cardiac muscle to contract.

Teamwork brings rapid results

Because the partners were able to draw on results already obtained for their respective subprojects, the development period required for the project has been unusually short. "The challenge now is to join the dots between these findings and to prepare them for application in the pacemaker," says Professor Heisterkamp of the REBIRTH unit on Laser Manipulation and Cellular Engineering, and the project's coordinator. As soon as this has been achieved, the scientists aim to develop a biohybrid defibrillator. This could reduce or even completely prevent long-term adverse effects of the treatment, such as scarring of the tissue. In addition, the technology developed can be extended to further application areas such as the skeletal muscles.

BioPACE: The partners

- LZH is responsible for coordinating the collaborative project BioPACE and is evaluating various optical technologies in terms of stimulation efficiency.
- MHH is making available its expertise in cell production, cardiac muscle generation and functional testing using small-animal models.
- LifePhotonic GmbH is providing the optical fibre technology.
- The Center for Applied Nanotechnology (CAN GmbH) is making available upconverting nanoparticles such as UCNPs and quantum dots.
- The University Hospital Bonn is using a transgenic animal model to explore potential applications for the cardiac muscle and skeletal muscles.

Open Day attracts 2,000 visitors

November 2016 was Science Month: REBIRTH joined forces with medics, scientists and trainers to present its work on 5 November.

13-year-old Paula holds a ventilated pig lung in her hands.

Clinicians, researchers and instructors presented interactive, hands-on medicine at an Open Day held by Hannover Medical School (MHH), which was the School's contribution to the fifth 'November of Science'. Among other things, MHH's nursing staff took this opportunity to provide a stimulating inside look into their highly varied jobs: a pig's lung was used to demonstrate how artificial ventilation works in humans. MHH's forensic scientists explained what they do, captivating their curious audience and, with real-life accounts of their lab work, exposing misconceptions resulting from many a TV crime show.

Specialists from the Department of Rehabilitative Medicine showed how motor training on a balance board can remedy balance problems, and people visiting the Institute of Human Genetics' stand were able to create their own family tree.

REBIRTH, too, presented its main research areas, enjoying in-depth conversations with visitors and using exhibits such as a microscope, a bioartificial lung and a decellularized pig heart valve. A poster for TECHNOBEAT, a project that has been funded by the European Union since 2016, explained how investigators headed up by Dr Robert Zweigerdt – of the REBIRTH unit on Mass Production and Purification of Recombinant Proteins – aim to produce billions of cells to replace tissue damaged in a heart attack, and hence help restore cardiac function.

Stem cell experts come together in Hannover

This fourth GSCN conference was held at MHH and financially supported by REBIRTH Cluster of Excellence.

Between 12 and 14 September 2016, the fourth International Annual Conference of the German Stem Cell Network (GSCN) welcomed more than 400 participants and 35 companies to Hannover Medical School (MHH). Over three full-on days, the scientific community shared its latest findings both orally and in the form of poster presentations. The event provided extensive networking opportunities allowing attendees to compare notes with existing collaborators and also to forge new connections.

On Wednesday afternoon, Professor Nils Hoppe, Professor Kai Wollert, Professor Thomas Thum and Dr Robert Zweigerdt presented their work within the REBIRTH Cluster of Excellence to national experts on stem cells at the REBIRTH Session.

In conversation (from left): GSCN-Business Manager Dr Daniel Besser, Professor Axel Haverich, MHH President Professor Christopher Baum, Prime Minister of Lower Saxony Stefan Weil and acting GSCN President Professor Ulrich Martin at the opening ceremony.

Maike Kosanke, who has been a doctoral student on the Ph.D. programme in Regenerative Sciences since 2015, received one of four GSCN poster awards. In the session headed 'Stem cells and ageing, genome stability and epigenetics', she presented her poster entitled 'Reprogramming enriches for subchromosomal variants that pre-exist at low frequency in parental cells'.

At the HAZ Forum: At a well-attended public event on Wednesday evening, Professors Axel Haverich, Nils Hoppe, Michael Manns, Tobias Cantz and Ulrich Martin presented advances in stem cell research to an interested lay audience.

GSCN Publication of the Year award goes to REBIRTH scientists

From left: Dr Martin Pacher, Professor Dr Michael Ott, Dr Guangqi Song, Dr Daniel Besser, Dr Amar Sharma and Professor Dr Ulrich Martin.

The German Stem Cell Network's (GSCN) award for Publication of the Year went to Dr Guangqi Song, Dr Martin Pacher, Dr Amar D. Sharma and Professor Michael Ott from MHH's Department of Gastroenterology, Hepatology and Endocrinology. It was for their research on the reprogramming of fibrosis-promoting myofibroblasts into hepatocytes, recently published in the journal *Cell Stem Cell* (see REBIRTH News 3/2016). At this year's GSCN conference held at MHH, the prize was presented by Professor Ulrich Martin, who presided over the event, and GSCN managing director Dr Daniel Besser. "I'm delighted for my young colleagues Guangqi Song and Martin Pacher, who are just starting out on their professional careers," says Professor Michael Ott, head of the Cell and Gene Therapy clinical research group at TWINCORE. Chinese scholarship-holder Dr Song has recently earned his doctorate (achieving summa cum laude status) in the natural sciences at MHH, and was recently invited to take up a post as a research scientist and university lecturer at the University of Fudan in Shanghai, China. "We'd like to have kept him in our work groups but his government-funded scholarship requires him to return to China for at least two years on completion of his project," explains Amar Sharma, who is head of the junior research group on MicroRNAs in Liver Regeneration and Song's direct supervisor. Pacher, a graduate of the Ph.D. programme in Regenerative Sciences, is now also no longer working at MHH, but in a pharmaceutical firm in Bavaria where he has been tasked with the quality control of molecular biological testing methods.

This outstanding work was carried out in close collaboration with REBIRTH researchers Professor Tobias Cantz (Translational Hepatology and Stem Cell Biology), Professor Axel Schambach (Experimental Haematology), Professor Doris Steinemann (Molecular Pathology) and Professor Hans Schöler (of the Max Planck Institute for Molecular Biomedicine in Münster). For REBIRTH coordinator Professor Axel Haverich, this accolade highlights the importance to Germany of research alliances like the REBIRTH Cluster of Excellence if it is to be remain a location for internationally competitive medical science research. "And, within REBIRTH, the chemistry within and among the various research groups seems to be right," he comments.

TECAS-ITN Orientation Week

From High School to University and Beyond

The 35 participants followed a five-day programme featuring keynote lectures by prominent academics, including REBIRTH coordinator Professor Dr Axel Haverich (Department of Cardiothoracic, Transplantation and Vascular Surgery [HTTG], Hannover Medical School [MHH]) and Professor Dr Hansjoachim Hackbarth (Institute of Animal Welfare and Behaviour, University of Veterinary Medicine Hannover, Foundation [TiHo]). There were also seminars, workshops, laboratory practicals and tours, as well as career mentoring sessions delivered by junior and senior academics and clinicians. This was the first time that the NIFE and the Hannover Unified Biobank had opened their doors for high-school pupils. An additional highlight of the five-day event was the group exercise. The students were divided into groups and they were then asked to prepare and deliver a

The 4th TECAS-ITN orientation week for high-school students was held from the 10th to the 14th of October 2016, at the NIFE – Lower Saxony Centre for Biomedical Engineering, Implant Research and Development. This year, the event was also open to students on the 'Studienkolleg' – a introductory course for foreign students at the Leibniz University of Hannover (LUH), who seized the opportunity to launch themselves onto a career path in academia and research.

podium presentation of a scientific publication of their choice. This activity was conducted under the supervision and guidance of a researcher who acted as the group mentor.

The school was organized by Dr Sotiris Korossis (of REBIRTH's Biohybrid Lung unit, HTTG, MHH) in collaboration with Professor Dr Birgit Glasmacher (Institute of Multiphase Processes, LUH) within the framework of the Marie Curie Initial Training Network-TECAS dissemination and outreach activities.

LISA: Studying in summer

Between 14 and 28 August 2016, Professor Tim Sparwasser (of TwinCore) and Dr Susanne Kruse (from the office of the Hannover Biomedical Research School) jointly organized the sixth Lower Saxony International Summer Academy (LISA) for Immunology (Inflammation, Regeneration and Immunity). Thirty-two students from 22 different countries were selected to attend. The researchers came

Women in science

Inaugural national conference a success.

Students, female scientists in early stages of their career and others in leadership positions: from 19 to 20 October 2016, 90 female researchers came together in Heidelberg for the first EMBL/DFG 'Women in Science' (WiS) Network Conference with the thematic focus 'From Genes, Cells and the Immune System towards Therapies'. This event provided the participants with an inspirational forum for sharing research, discussing career opportunities and networking. In talks, they reported on genetic, cellular and immunological mechanisms and immunotherapies, as well as on progress from all developmental phases of basic research as far as clinical development. The presentations were incorporated into structured networking events.

"Following similar but smaller-scale meetings in Bonn, Hannover and Munich in 2015, this event held at the Advanced Training Centre of the European Molecular Biology Laboratory (EMBL) was Germany's first national WiS conference," says Professor Renata Stripecke of the REBIRTH unit called Regenerative Immune Therapy Applied. This unit organized the event in conjunction with Professor Irmgard Förster of the University of Bonn and Dr Cecile Gouttefangeas from the University of Tübingen. The conference was funded by nine DFG Collaborative Research Centres supported by the German Research Foundation (DFG).

from Hannover Medical School (MHH), TwinCore and the Fraunhofer Institute of Toxicology and Experimental Medicine (ITEM).

The programme included an intensive week of lectures and workshops followed by three weeks of hands-on laboratory training, including introduction to various instruments.

Additionally, outstanding international lecturers such as Michael Sixt of the Vienna-based Institute of Science and Technology Austria, Paola Romgnoli from the Centre of Pathophysiology of Toulouse Purpan, Florent Ginhoux of the Singapore Immunology Network (SIgN), and Doreen Cantrell from the University of Dundee gave lectures and had discussions with the LISA students. The participants were also able to take part in social activities such as a city tour, barbecue, a fireworks display and a visit to the GOP variety theatre. The Academy was kindly supported by HBRS, REBIRTH, EFIS and several biotech companies. “The feedback was extremely positive, and so we’re already planning another LISA event for next year,” says Dr Kruse.

Participants at the Summer Academy.

Participants at the EMBL/DFG WiS Network Conference.

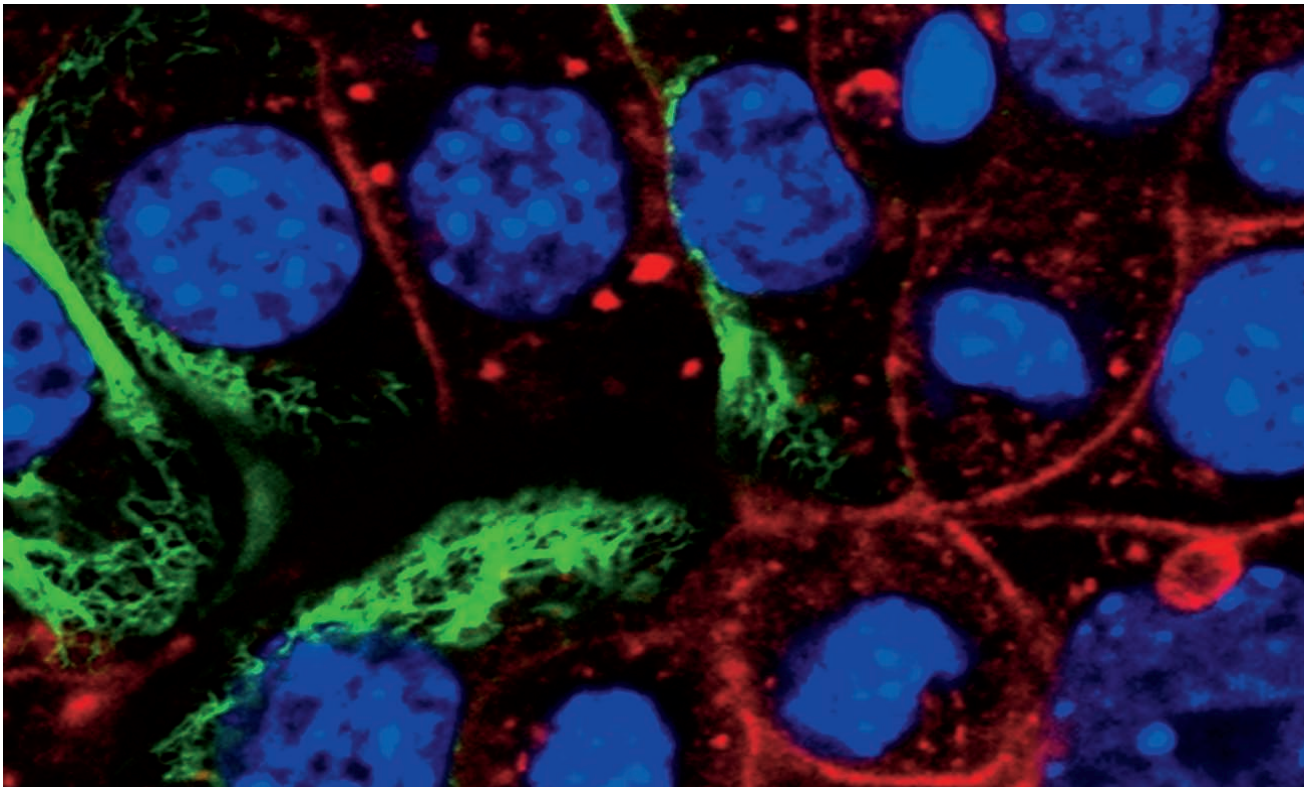
REBIRTH doctoral students win accolade

Every year, Hannover Biomedical Research School (HBRS) honours the best doctoral thesis at its event to mark the new academic year. In 2016 it was held on 17 October, and not one but three HBRS awards were presented, two of which went to doctoral students in the REBIRTH Cluster of Excellence.

Dr Janika Viereck, who is alumna of the Ph.D. programme in Regenerative Sciences, received the accolade for her doctoral thesis entitled 'Non-coding RNAs as "theranostics" in heart, lung and circulation'. She did her research work within the REBIRTH unit on miRNA in Myocardial Regeneration, which is led by Professor Thomas Thum. In her thesis, she identified a previously unknown long non-coding ribonucleic acid (lncRNA), which plays a key role in the development of cardiac insufficiency. Pharmacological inhibition of this lncRNA made it possible to reverse pathological remodelling processes in the heart and to considerable improve its function (REBIRTH News 1/16). New therapeutic approaches are of great importance for this condition, as existing treatment options only slow the progression of the disease but are unable to halt or reverse it.

Dr Dakai Yang, who is alumna of the Ph.D. programme in Molecular Medicine, received the HBRS award for her thesis entitled 'Identification of microRNA-125b-5p as a key regulator of liver regeneration and acute liver failure'. As part of the team from the REBIRTH unit on miRNA in Liver Regeneration, headed up by Dr Amar Sharma, she investigated 302 microRNAs that occur in both mice and humans as to their role in acute liver failure. She discovered a microRNA that prevents this acute condition (REBIRTH News 3/2016). Acute liver failure may occur as a result of viral infection, pharmaceutical intolerance or poisoning (following mushroom consumption, for example). In many cases, the lives of the patients affected can be saved only by a liver transplant, as effective drugs have not yet been developed.

The award-winners:
Dr Dakai Yang (left) and Dr Janika Viereck (right) with Professor Reinhold E. Schmidt.



The award winning picture.

A spell abroad leads to unexpected success

Masters student co-authors *Nature* publication.

While doing his Master's thesis, which he completed in biomedicine at Hannover Medical School (MHH) in 2015, an Erasmus+ scholarship took Sebastian Theobald to the UK's prestigious Cambridge University for a two-month stint. "At Cambridge, I worked within the MRC Cancer Centre in the laboratory of Dr Christian Frezza, where I contributed to four different projects," says Theobald. In one of these projects, namely that on fumarate as an oncometabolite in the epithelial-to-mesenchymal transition (EMT), Theobald helped postdoctoral researcher Dr Marco Sciacovelli to analyse – by means of confocal microscopy – the EMT process associated with cancer formation in various knockout cell lines. Again using confocal microscopy, Theobald also investigated mouse cells as to their methylation status. "These data have now resulted in my co-authorship of a publication that appeared in the journal *Nature* in August 2016," enthuses the biomedical specialist who won the MRC Cancer Centre's 'Picture of the Month' award for one of his images. "I really enjoyed my time in Cambridge and am still in touch with the colleagues I met there – in fact we've already visited each other several times."

Sebastian Theobald has, since October 2015, been a doctoral student on the Ph.D. programme in Regenerative Sciences. He conducts his research in the lab of Professor Renata Stripecke of the REBIRTH unit 'Regenerative Immune Therapies Applied', where he had already worked as a research assistant while doing his Master's.

Ph.D. Programme Regenerative Sciences

Welcome to our new intake of students!

The 10th year of the Ph.D. programme in Regenerative Sciences has seen a big intake, with 19 new doctoral students having started in October. Over the next three years, these 13 women and six men will be researching aspects of regeneration. They are from 10 different countries, three of which are represented on the programme for the first time: Morocco (Houda Ichati), Ghana (Abulai Usman) and the USA (Anais Sahabian, an American with Romanian roots). All three of them are doing their doctoral thesis in different research groups at the Leibniz Research Laboratories for Biotechnology and Artificial Organs (LEBAO).

Alongside its internationality, an important feature of the Ph.D. programme is interdisciplinarity. "That's why we're especially pleased that, once more, veterinarians have joined the programme – two of them, in fact," says Dr Daniela Pelz, its coordinator. Hendrik Sake is based at the FLI's Institute of Farm Animal Genetics in Mariensee, and Annika Heß works in the research group led by Dr Jens Bankstahl at Hannover Medical School's (MHH) Department of Nuclear Medicine. The new students also include a medical doctor, Julia Meier, who aspires to the challenging career of a clinical scientist. She is obtaining her medical speciality in MHH's Department of Cardiacthoracic, Transplantation and Vascular Surgery (HTTG), and completing her scientific training at the Lower Saxony Centre for Biomedical Engineering, Implant Research and Development (NIFE) in the work group headed up by Dr Ulrike Böer and Professor Mathias Wilhelmi.

The new NIFE research building on Stadtfelddamm, which the scientists did not move into until early in 2016, is also home to another project: Sonja Johannsmeier is doing research there in the group led by Dr Dag Heinemann, who himself earned his doctorate on the Ph.D. programme in Regenerative Sciences. Dr Heinemann is not the only alumnus of the Ph.D. programme who has 'changed sides': Dr Nico Lachmann, too, is supervising two doctoral students at the Institute for Experimental Haematology (IEH). Also new as a supervisor on the Ph.D. programme is Professor Hildegard Büning, who holds a professorship in the infection biology of gene transfer at IEH. She joined MHH from University Hospital Cologne in March 2015 and has already served as a co-supervisor on the Ph.D. programme.

The REBIRTH management welcomes all the new Ph.D. students and their supervisors and wishes them every success and an enjoyable time on the doctoral programme!

Apply now for 2017!

We will be receiving applications for the 2017 intake from 1 December (as in previous years) via the online portal: https://hbrs.opencampus.net. Dr Pelz and Mariam Kujenya will be happy to answer enquiries at phd-regsci@mh-hannover.de.

What are you working on and why?

The liver is a vital organ in vertebrates that supports almost every other organ and is best known for its remarkable regenerative capacity and detoxification function. However, there are multiple common causes of liver failure, such as hepatitis, fatty liver disease or liver cancer, which leave the patient in need of a partial or complete liver replacement or support. Because of the shortage of transplantable donor organs, our focus is on *in vitro* expansion of hepatocytes. To avoid the loss of liver specific functions, which is the main problem when expanding liver cells in the lab, we genetically manipulate key hepatic signalling pathways thereby restoring these functions in hepatocytes. These modified hepatocytes are much better at mimicking liver cells *in vivo* than conventional cell culture systems are, making them far more suitable for liver replacement approaches, temporary liver assist devices during acute liver failure, and also for basic and applied research.

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

I always very much liked the idea of multidisciplinary research in regenerative approaches; working together with and communicating your ideas to other scientists is something I genuinely enjoy. And of the – surprisingly few – European structured Ph.D. programmes that focus on Regenerative Sciences, I feel that REBIRTH offers the best approach to multidisciplinarity.

Ph.D. Programme Regenerative Sciences

Who is Who

Tom Wahlicht *(26) from Germany, REBIRTH Unit 4.4 – Rational Cell Engineering*

Did you always want to become a scientist?

My career aspirations ranged from becoming 'a boss' in kindergarten and an archaeologist in elementary school to a doctor in early secondary school, with the obligatory fire fighter thrown into the mix at some point as well. But as soon as I got the first proper insights into biology I was fascinated by the idea of understanding the inner workings of living organisms. So at that point it was pretty clear I was becoming a scientist and my fascination has not changed since.

What (crazy / realistic) innovation will have come out on top by 2030?

Can someone please already invent and implement a smartphone airbag that prevents shattered smartphone displays? But on a more serious note, I hope that by 2030 battery technology will have made some big steps forward in terms of costs, energy density, safety and charge/discharge cycles. I think this would benefit all aspects of a modern society.

- More affordable electric cars with a longer range would replace combustion engine cars;
- the ability to store energy from regenerative sources in a space-efficient manner for later use;
- and fewer battery replacement operations for patients that rely on intracorporeal electronic devices – pacemaker patients, for example – are things that come to my mind.

Scientific research at the Library

A placement with a difference

The British Library in London is the largest in the world. Apart from holding all kinds of items – including manuscripts, maps, patents, sound recordings and, of course, books – the Library also supports research in various academic disciplines and fosters public engagement with knowledge and research. It is in this spirit that the Science Team organizes its 'TalkScience' series of public events, where an interested audience has the chance to get involved in discussion on a topical science issue with a panel of experts. The latest instalment of 'TalkScience' on 13 October was developed by Mandy Kleinsorge, a Ph.D. student in the REBIRTH unit on Translational Hepatology and Stem Cell Biology, during a three-month placement with the Library. Being interested in research into animal alternatives, she collaborated with the UK 'National Centre for the Replacement, Refinement & Reduction of Animals in Research' (NC3Rs) to arrange a public discussion on the '3Rs'.

Stephen Holgate (of Southampton University and Board Chair of the NC3Rs) chaired the event, which featured a panel of prominent speakers: Robin Williams (Royal Holloway), Sally Robinson (AstraZeneca) and Robin Lovell-Badge (Francis Crick Institute). The speakers introduced the audience to their perspectives on the issue of animals in research. They spoke about *in vitro* methods that are already established and do not depend on animals, and about efforts to reduce the use and improve the welfare of those animals still needed in research. "During the discussion it became apparent that, in this field, there is a lack of acceptance of alternatives to animals, with reviewers in funding and publication continuing to ask for animal models first," Mandy Kleinsorge reports. "Furthermore, studies using animals need to be designed more carefully with robust biostatistics and ensuring the highest standards of welfare in the handling of animals." It was also stressed that there is a need for more openness in animal research, as properly explaining it will help with public understanding.

Mandy found the experience she gained during this placement most enriching: "I would like to encourage Ph.D. students to – as it were – look over the rim of their tea cup, too. Getting such insights into the communication of science and public engagement can be useful for careers both inside and outside of academia."