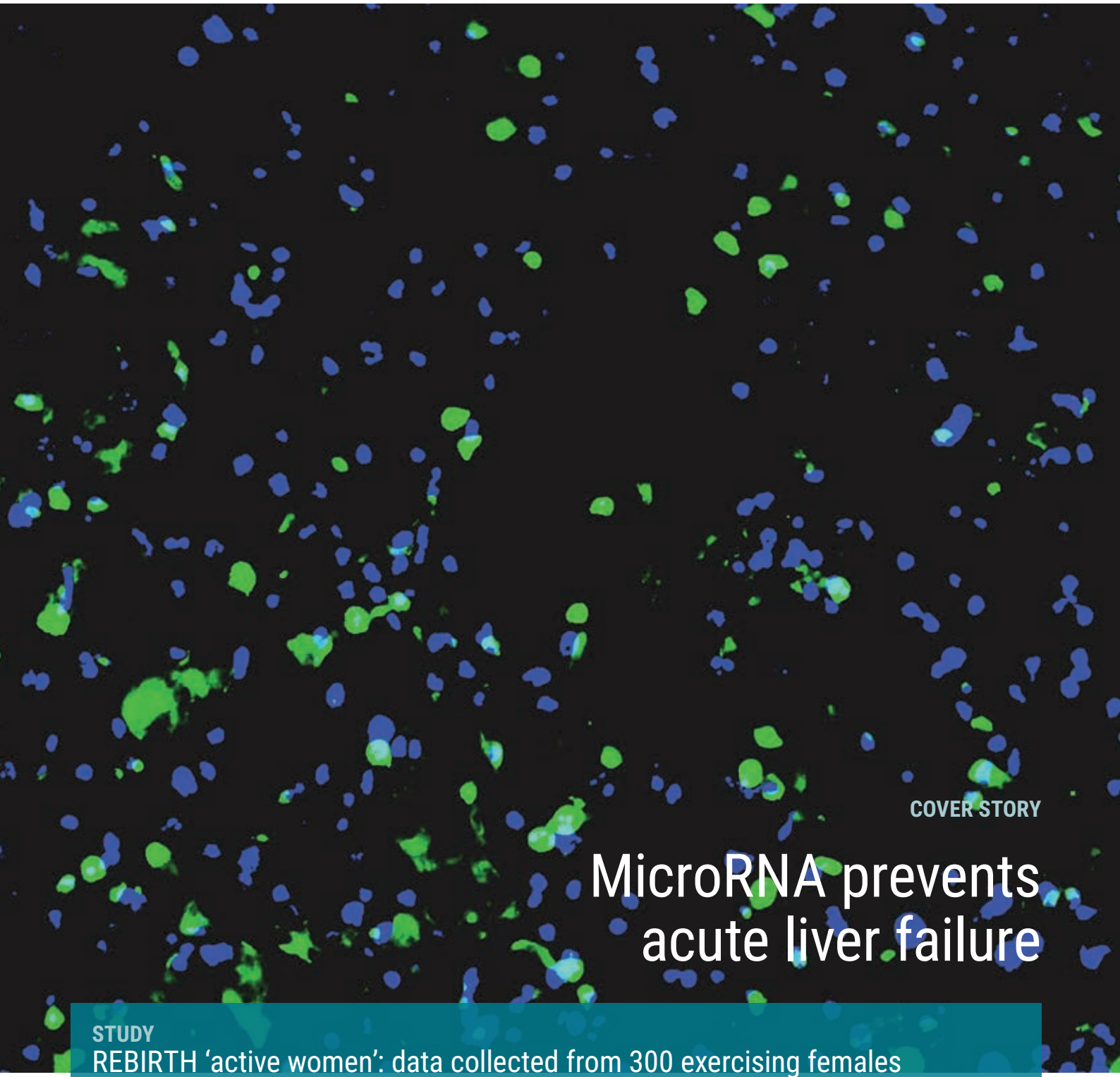
rebirth news 3 SEPTEMBER 2016



COVER STORY

MicroRNA prevents acute liver failure

STUDY

REBIRTH 'active women': data collected from 300 exercising females

FUNDING

Six million euros in funding for clinical researchers

INTERNATIONAL EXCHANGE

DAAD RISE Germany: Research Internships in Science and Engineering

Latest Publications

Blood platelets go 'under cover'

In this publication, the researchers demonstrate the ability to generate HLA-universal megakaryocytes and blood platelets. These megakaryocytes were able to escape the exogenous (i.e. of foreign origin) humoral and cellular immune response. In a mouse model of platelet transfusion, too, the megakaryocytes were able to survive and, under adverse conditions – in the presence of anti-HLA antibodies – produce platelets. The *in vitro* production could conceivably make a platelet donation obsolete.

Publication

Borger AK, Eicke D, Wolf C, Gras C, Aufderbeck S, Schulze K, Engels L, Eiz-Vesper B, Schambach A, Guzman CA, Lachmann N, Moritz T, Martin U, Blasczyk R, Figueiredo C. Generation of HLA-Universal Ipscs-Derived Megakaryocytes and Platelets for Survival under Refractoriness Conditions. *Mol Med*. 2016;22. Epub 2016/06/05.

Structure of an actomyosin complex

In muscles, the cyclical interplay between overlapping actin and myosin generates force and movement. Specialized, slightly modified versions of actin and myosin also occur in our other body cells, where they perform transporting functions. Malfunctions of these transport processes are responsible for a large number of neurodegenerative conditions, and are observed in cancer cells. This paper describes one of these transporter complexes at near-atomic resolution. These findings provide important information about the regulation of transporter complexes and will allow to develop new therapeutic approaches.

Publication

von der Ecken J, Heissler SM, Pathan-Chhatbar S, Manstein DJ, Raunser S. Cryo-Em Structure of a Human Cytoplasmic Actomyosin Complex at near-Atomic Resolution. *Nature*. 2016;534(7609):724-8. Epub 2016/06/22.

Macrophages: understanding diseases

Research into rare hereditary diseases such as pulmonary alveolar proteinosis (PAP) is often complicated by a lack of cellular material. This publication describes a protocol that allows macrophages to be obtained from healthy and disease-specific murine induced pluripotent stem cells (iPS cells) that are both comparable with macrophages of the bone marrow. The cellular defects affecting alveolar macrophages were able to be faithfully recapitulated in the *in vitro* system described using macrophages derived from iPS cells. Such macrophages are, therefore, well suited for use as an *in vitro* model and for discovering new therapeutic approaches.

Publication

Mucci A, Kunkiel J, Suzuki T, Brennig S, Glage S, Kuhnel MP, Ackermann M, Happle C, Kuhn A, Schambach A, Trapnell BC, Hansen G, Moritz T, Lachmann N. Murine iPSC-Derived Macrophages as a Tool for Disease Modeling of Hereditary Pulmonary Alveolar Proteinosis Due to Csf2rb Deficiency. *Stem Cell Reports*. 2016;7(2):292-305. Epub 2016/07/28.

PPCM: a practical guide to treatment

Acute heart failure caused by peripartum cardiomyopathy (PPCM) is a challenge for physicians. Especially where patients are still pregnant, their doctors always need to have in mind the health of both mother and foetus. The European Society of Cardiology's (ESC) Study Group on PPCM has issued a comprehensive guide for the medics involved. It clearly defines the symptoms and provides information about how to properly diagnose and treat the various types of heart failure associated with pregnancy.

Publication

Bauersachs J, Arrigo M, Hilfiker-Kleiner D, Veltmann C, Coats AJ, Crespo-Leiro MG, De Boer RA, van der Meer P, Maack C, Mouquet F, Petrie MC, Piepoli MF, Regitz-Zagrosek V, Schaufelberger M, Seferovic P, Tavazzi L, Ruschitzka F, Mebazaa A, Sliwa K. Current Management of Patients with Severe Acute Peripartum Cardiomyopathy: Practical Guidance from the Heart Failure Association of the European Society of Cardiology Study Group on Peripartum Cardiomyopathy. Lid – 10.1002/Ejhf.586 [Doi] Fau - Bauersachs, Johann. (1879-0844 (Electronic)).

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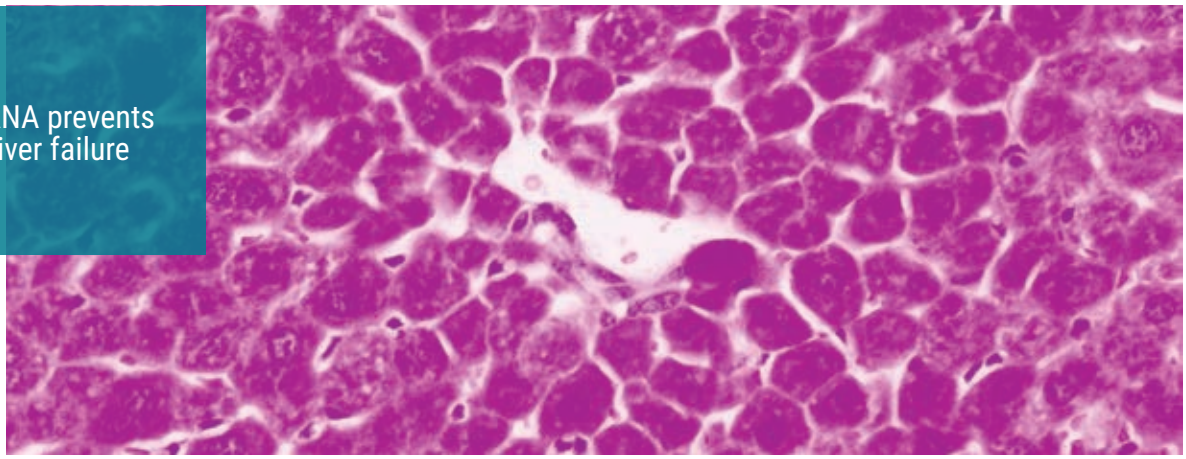

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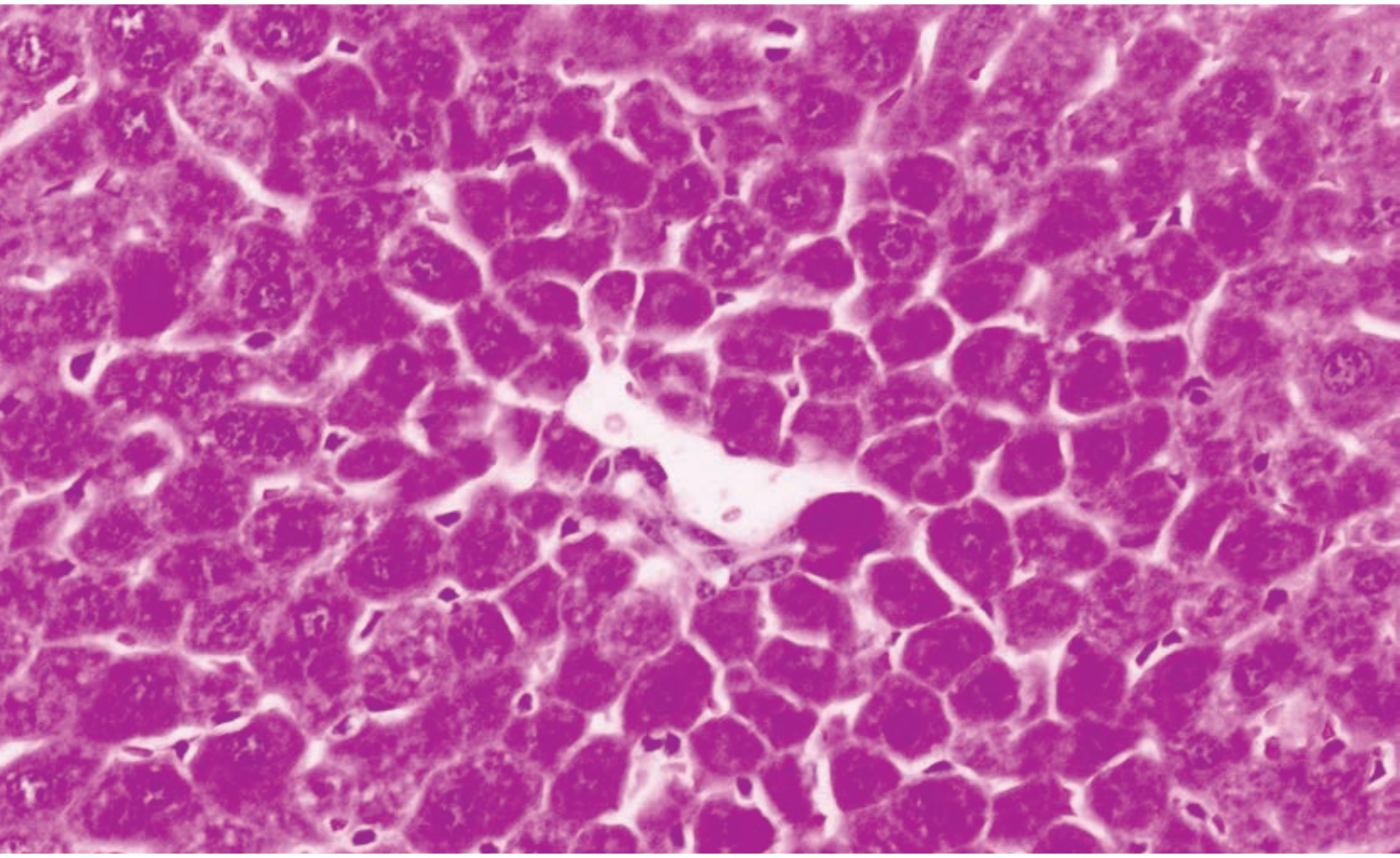
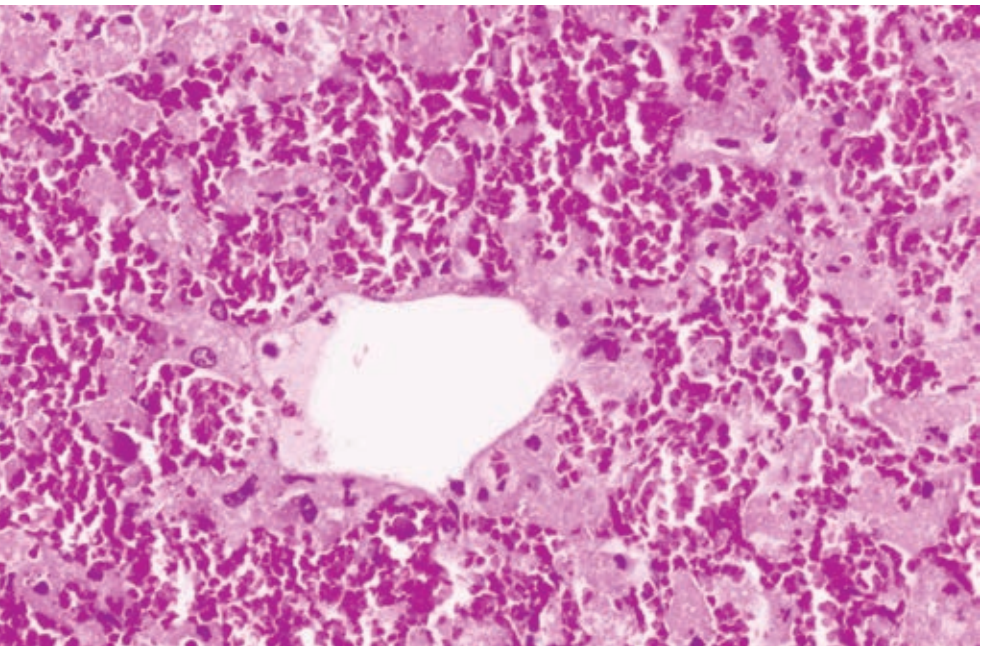
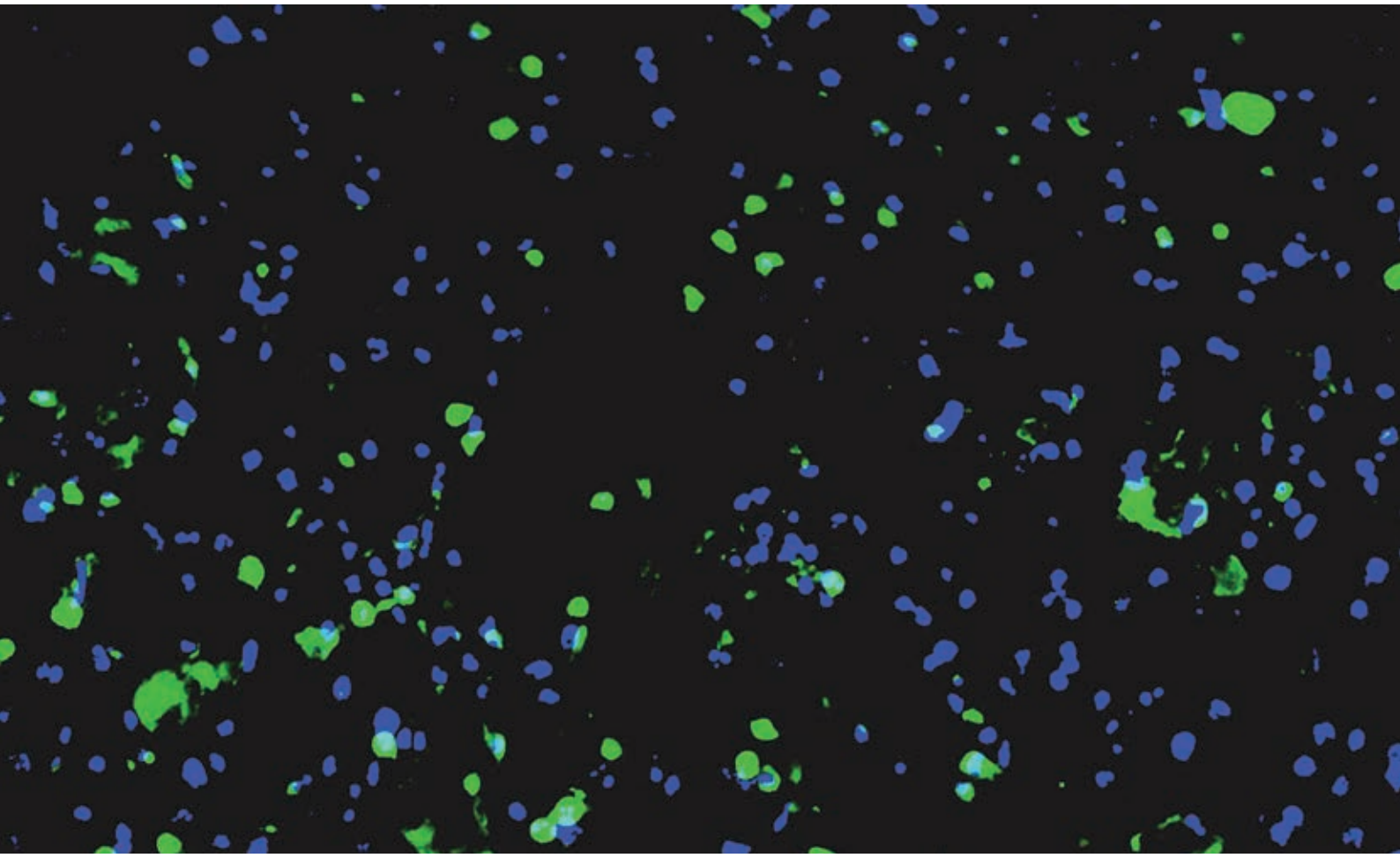




Histological analyses revealed reduced acute liver failure in mice injected with mircoRNA-125b-5p (top) compared to control mice (bottom).

Cells treated with MicroRNA-125b-5p. MicroRNA mitigates liver failure by preventing cell death (green).



MicroRNA prevents acute liver failure

Acute liver failure can be caused by viruses, drug intolerance or poisoning (following mushroom consumption, for example). In many cases, a liver transplant is the only way to save the patient's life, as effective drugs have not yet been developed.

A team of investigators at the REBIRTH Cluster of Excellence and Collaborative Research Centre (SFB) 738 at Hannover Medical School (MHH) has now identified a short ribonucleic acid (microRNA) that may prevent acute liver failure. The researchers were also able to identify the mechanism involved.

"In a mouse model, the injection of microRNA-125b-5p prevents the death of the liver cells and hence liver failure," explains Dr Amar Deep Sharma. "This means we have found a potential new treatment for acute liver failure," adds Professor Michael Ott.

Doctoral student Dakai Yang has investigated 302 microRNAs that occur in both mice and humans as to their role in acute liver failure. "The advantage of microRNAs is that

Honoured by the Queen

He has seen a lot in his time, garnered many accolades and met many prominent people. However, what happened on 14 July was a first for Professor Axel Haverich: the director of Hannover Medical School's (MHH) Department of Cardiac, Thoracic, Transplantation and Vascular Surgery (HTTG) was honoured by Queen Elizabeth II. Every year, to coincide with Her Majesty's birthday, the Queen's Anniversary Awards are presented for achievements in different realms of life. Together with Scottish company Vascutek, Haverich had the privilege of receiving this prize at Buckingham Palace for the development of a procedure known as the 'frozen elephant trunk'. For many years now, this innovation has made a second major operation of the thoracic aorta unnecessary. Haverich's brainchild, the idea was adopted by Vascutek. "This was a great honour for me – and a really special moment," stressed Haverich. Evidently, even after 20 years in his prestigious post, there are still some surprises in store for him.

from left: Michael Ott, Dakai Yang, Amar Deep Sharma, Tobias Cantz

they can be produced in industrial and therapeutic quantities and are easy to apply through a vein. However, there is still some way to go before they can be used in humans," says Professor Tobias Cantz. "The next step will involve our attempting to determine the ideal concentration of microRNA as a therapeutic agent."

The four scientists at MHH's Department of Gastroenterology, Hepatology and Endocrinology published their findings in the journal *Nature Communications*. "This outstanding work is the result of pooled expertise from different research teams within the Cluster of Excellence and SFB 738, and demonstrates MHH's particular capability in translational research," says Professor Manns, head of the above-mentioned department and coordinator of SFB 738.

Publication:
Yang D, Yuan Q, Balakrishnan A, Bantel H, Klusmann JH, Manns MP, Ott M, Cantz T, Sharma AD. Microrna-125b-5p Mimic Inhibits Acute Liver Failure. Nat Commun. *2016;7:11916. Epub 2016/06/24.*

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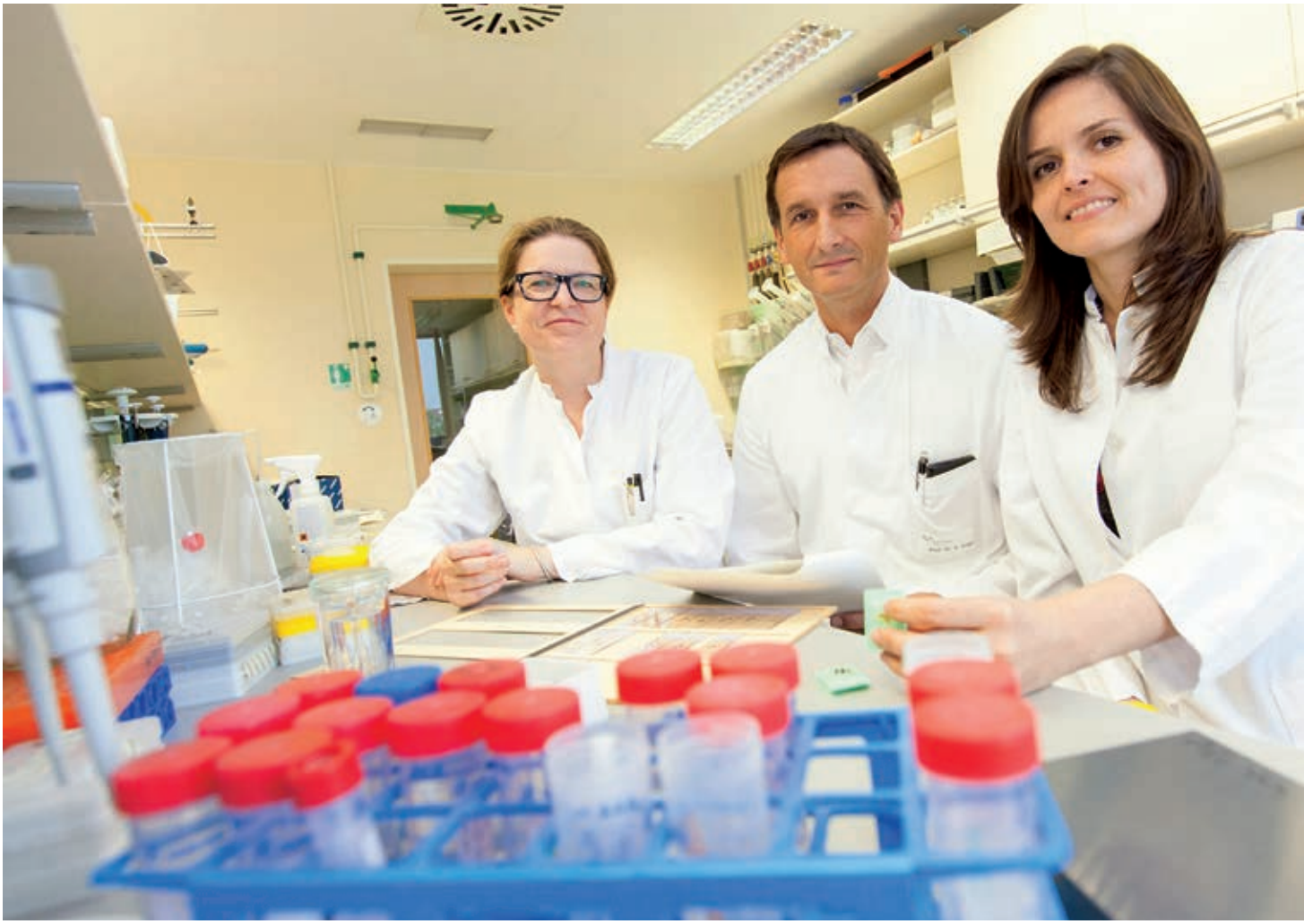
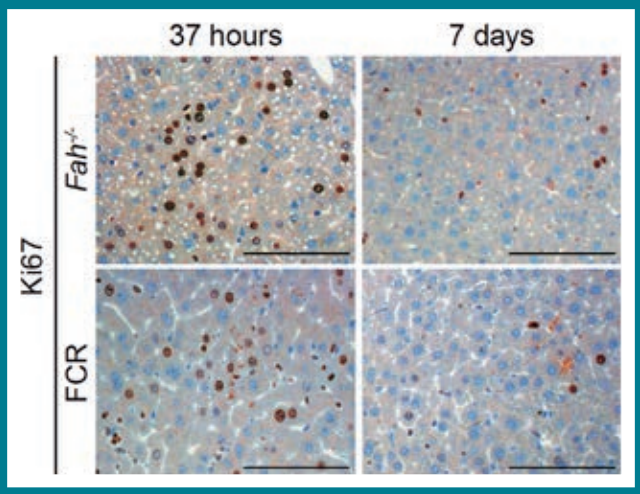


from left: Dr Silke Marhenke, Professor Arndt Vogel and Dr Laura Elisa Buitrago-Molina analysing the results.

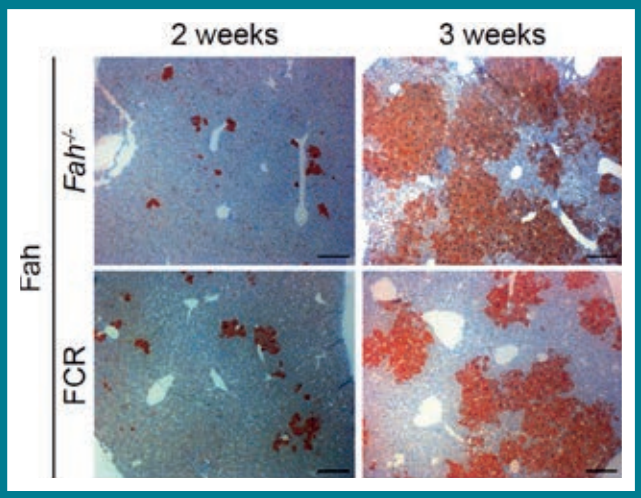
The immune system: a double-edged sword

Fatty liver, excessive alcohol consumption or viruses can cause infections of the liver that may lead to chronic inflammation and subsequently to cirrhosis and cancer of this organ. Researchers at Hannover Medical School's (MHH) Department of Gastroenterology, Hepatology and Endocrinology have now uncovered the role of the immune system in the development of liver cancer.

The team that makes up the REBIRTH unit on Molecular Mechanisms of Endogenous Liver Regeneration, headed by Professor Arndt Vogel, was able to demonstrate in a mouse model that, while the rodents' immune system protects against acute liver failure at the early stages of chronic liver disease, at later stages it is significantly involved in liver damage and thus contributes to carcinogenesis. "In particular, the $CD8^+$-T-cells of the acquired immune system, and the lymphotoxin-β signalling pathway that is activated in many autoimmune and chronic conditions, are key mediators in the development of liver cancer," medical scientist Professor Vogel explains. A specific chemopreventive therapy, with which the immune system would be closely regulated, would therefore be a promising approach to safeguarding patients with chronic liver disease



Liver regeneration following partial liver resection in mice with and without an immune system.



Liver repopulation following liver cell transplantation.

from cancer while at the same time ensuring protection via the immune system. "A hopeful sign is that, in other clinical contexts, there have already been initial studies with an inhibitor of lymphotoxin-β that is worth considering as a drug for chemopreventive treatment," adds Professor Vogel. First, however, the investigators need to conduct a clinical trial of their own to prove that a therapy of this kind is suitable in humans. The team led by Professor Vogelhas published its findings in the periodical *Cancer Cell*.

Reaching this conclusion was a multi-step process for the researchers. First they found out that mice which lacked an immune system and had a chronic liver disease died of acute liver failure at an early stage. This is not the case in mice with an intact immune system. They then used various genetic models to investigate the influence of immune cells on liver damage and discovered that, whereas $CD8^+$-T-cells prevent acute liver failure, at a later stage they play a key part in liver damage and in the development of liver fibrosis. In further pharmacological approaches, the scientists then showed that the lymphotoxin-β signalling pathway assumes a particularly important role in carcinogenesis.

Immune system does not influence liver regeneration

In this connection, the researchers also looked at the effect of the immune system on liver regeneration. They first analysed whether differences were evident in the basal rate of regeneration in mice. As a result of the more serious liver damage, stronger regeneration was found in those mice with an intact immune system. Interestingly, after a partial liver resection, there was no difference in liver regeneration between liver-damaged mice with and without an immune system. In another approach, the investigators transplanted healthy liver cells into the livers of liver-damaged mice with and without an immune system. Here, too, similar repopulation of liver cells in the recipient livers was observed. "We can therefore assume that the immune system has no influence on liver regeneration in our model of chronic liver damage," says Professor Vogel.

Endig J, Buitrago-Molina LE, Marhenke S, Reisinger F, Saborowski A, Schutt J, Limbourg F, Konecke C, Schreder A, Michael A, Misslitz AC, Healy ME, Geffers R, Clavel T, Haller D, Unger K, Finegold M, Weber A, Manns MP, Longerich T, Heikenwalder M, Vogel A. Dual Role of the Adaptive Immune System in Liver Injury and Hepatocellular Carcinoma Development. Cancer Cell. *2016;30(2):308-23. Epub 2016/08/02.*

Why iron is good for the heart

People with heart failure (cardiac insufficiency) often suffer from iron deficiency. When they are treated with this element, these patients feel better and are more resilient; they do not need to go to hospital as often and may well live longer. Scientists at Hannover Medical School's (MHH) Department of Cardiology and Angiology have now discovered why.

from left: Kai C. Wollert, Tibor Kempf

They have described the underlying mechanism and published it in the renowned *European Heart Journal*. In so doing, they have explained not only the positive impact of iron therapy that doctors and sufferers alike have long observed, but also why iron is so important for cardiac function.

A team of scientists led by Professors Tibor Kempf and Kai Wollert (REBIRTH unit on Secreted Factors and Non-Cell-Based Strategies for Cardiac Regeneration) deactivated the Irp proteins in the cardiac muscle cells of mice – the proteins that regulate iron levels in these cells.

The hearts of these mice became iron-deficient, which was not the case for the blood and other organs. Under resting conditions the animals appeared healthy, but during physical strain their hearts were unable to increase their pumping function; following heart attack (myocardial infarction), the animals developed marked cardiac insufficiency. The cause was excessively low energy production in the mitochondria. When the MHH researchers administered iron to the mice, they were able to replenish their iron reserves in the heart, the cardiac muscle cells once again produced enough energy, and heart function normalized.

Cardiac insufficiency is among the most frequent causes of death in Germany and is caused by heart attack, high blood pressure or defective heart valves. Other findings of the MHH researchers show that reduced activity of the IRP proteins is another factor. "Thus, iron deficiency is not only indicative of a poor prognosis, but also the cause of the poor prognosis in individuals with heart failure. And it's easy to remedy," stresses Professor Johann Bauersachs, director of MHH's Department of Cardiology and Angiology.

New guidelines introduced this year recommend that physicians prescribe iron to patients with cardiac insufficiency who are also deficient in this element. Several clinical trials are currently investigating whether supplementation with iron can do more than merely improve symptoms, namely extend sufferers' lives.

Publication

Haddad S, Wang Y, Galy B, Korf-Klingebiel M, Hirsch V, Baru AM, Rostami F, Reboll MR, Heineke J, Flogel U, Groos S, Renner A, Toischer K, Zimmermann F, Engeli S, Jordan J, Bauersachs J, Hentze MW, Wollert KC, Kempf T. Iron-Regulatory Proteins Secure Iron Availability in Cardiomyocytes to Prevent Heart Failure. Eur Heart J. *2016. Epub 2016/08/23.*

Awakening interest in research

How is the Zika virus detected in the blood? Is 'biohydrogen' suitable as a renewable fuel source? From 25 to 29 July 2016, 11 upper-school pupils in teams of two to four explored these and other questions from the worlds of medicine, biotechnology, biochemistry and life science. This was the fifth such 'Research Week' (Forscherwoche).

Pupils were enabled to explore in greater depth subject matter raised during school science classes, and to gain experience at experimentation.

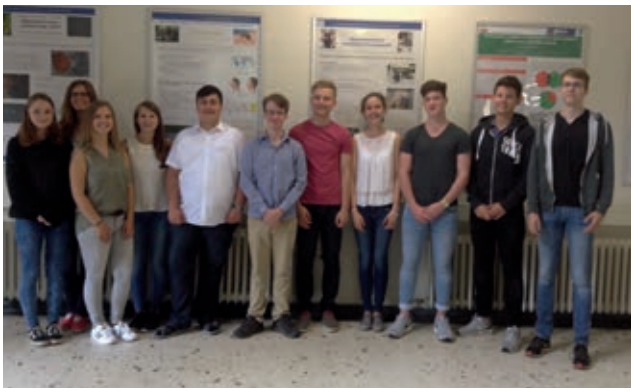
"Most of the pupils were very enthusiastic about their topic," reports Annabell Wähner, who supervised the group. She herself was, until the end of August, on a 'Research Gap Year' (FWJ) within the REBIRTH unit on Translational Hepatology and Stem Cell Biology. "I especially enjoyed being able to pass on many of the things I have learned during the past year."

"This year's participants were already able to use pipettes and knew a lot in general – in some cases a great deal – already," adds Research Week coordinator and supervisor Hendrika van Waveren.

"So we focus particularly on learning communication skills to prepare for a later career in science and engineering,

Partners

As in previous years, and in collaboration with the REBIRTH Cluster of Excellence, the University of Hannover's Faculty of Natural Sciences and the Life Science Lab at the City of Hannover's School Biology Centre invited upper-school pupils to experiment in the interdisciplinary field of life science. This year's participants came mainly from the Hannover region, but also from North Rhine-Westphalia.



such as researching information, learning communication patterns, and appropriate presentation of completed projects."

Many Research Week 'alumni' are now studying in a career area portrayed during one of the past Research Weeks, and report that the knowledge acquired in the school lab had been very helpful for their degrees.

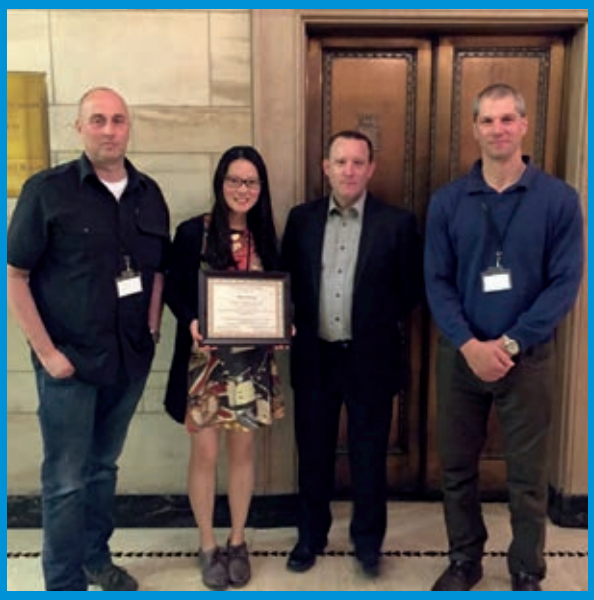
Can the bespectacled sheep be saved?

The Research Week always results in promising projects for the 'Jugend Forscht' competition aimed at young researchers. In the spring of 2016, a genetic study of the Jezersko–Solčava sheep (aka: Carinthian sheep, in German: Brillenschaf, 'bespectacled sheep') made it to the national finals in Paderborn.

Ph.D. student wins prestigious accolade

The 53rd Annual Meeting of the Society for Cryobiology was held this year from 23 to 27 July 2016 in Ottawa, Canada. The conference covered basic cryobiology research in animal and plant sciences, as well as applications for preservation of organs, tissues and cells.

Miao Zhang, a Ph.D. student on the HBRS Ph.D. programme in Regenerative Sciences, received both a travel award allowing her to attend the meeting and the prestigious Peter L. Steponkus Crystal Award for best student research and oral presentation (total prize money $2,800). She presented studies on the uptake of membrane-impermeable protective molecules such as trehalose into mammalian cells at supra- and subzero temperatures used for non-toxic cryopreservation and preservation of DNA in freeze-dried cells.



from left: Wim Wolkers, Miao Zhang, Jason Acker (President of the Society for Cryobiology) und John Bischof (Alexander von Humboldt fellow).

Participating departments at MHH

- Sports Medicine
- Cardiac, Thoracic, Transplantation and Vascular Surgery (HTTG)
- Cardiology and Angiology
- Gynaecology
- Paediatric Nephrology, Hepatology and Metabolic Disorders
- Dental Prosthetics
- Hannover Clinical Trial Center (HCTC)
- Biometrics

REBIRTH 'active women': data collected from 300 exercising females

Almost 300 women over 45 years of age, who had not previously taken part in regular physical activity, have participated in the REBIRTH 'active women' study over the last three years.

For six months, they exercised for an average of 30 minutes a day. The physicians supervising them examined their performance and state of health, assessed their periodontal status (a marker of chronic inflammation) and took blood samples. They conducted two thorough medicals, one at the beginning and one at the end of the six-month training intervention, as well as other tests during the trial. "The subjects in both the active group – i.e. the exercising ones – and the inactive control group have now completed the programme," says sports scientist Julian Eigendorf, the study's coordinator from the Institute of Sports Medicine. He is currently still collating the data obtained from six different clinical departments. For example, the REBIRTH unit on Senescence in Vascular Regeneration headed by Professor Anette Melk is still investigating the length of telomeres in the various blood samples to find out how exercise affects biological age. "Without assistance from the Hannover Clinical Trial Center (HCTC), it would have been virtually impossible for us to handle the huge volume of data," Eigendorf notes. "I now hope that we'll have the final results by early 2017 at the latest."

The HCTC is helping with the trial, providing ongoing assistance with both data management and monitoring. "For our team, this is one of the typical studies where our experience enables us to provide rapid and effective help with managing the study," says Professor Heiko von der Leyen, who heads both the HCTC and the REBIRTH Unit on Clinical Trial Management.

For data management purposes, Barbara Neuhaus and her team at HCTC programmed a suitable data entry screen within the MARVIN database system – a system validated to the GAMP-5 standard – enabling all the data to be reliably collected and making the analysis available more easily. "Some measuring instruments, such as those for pulmonary function testing and spirometry, outputted the data in the form of a txt document," explains Ms Barbara Neuhaus, head of the data management team at HCTC. She helped Eigendorf to amalgamate the data entered into MARVIN with those from the measurement devices, and to transmit them in a format widely used for statistical analysis. "It's not normally the case that data are imported directly from the measuring instruments. This was something of a challenge, but certainly an interesting one!"

As part of the monitoring, HCTC's Juliane Neubronner checked (on a random basis) whether the data entered in MARVIN by the Sports Medicine team matched those in the patients' files, whether declarations of consent had been obtained and the treatment corresponded with the original plan. "Monitoring is crucial to the quality of this study," says HCTC's monitor Neubronner. She also gave Eigendorf handy hints and tips as to practical improvements the team can make as they continue the trial.

Post-trial follow-up

Now, two years on, the 'REBIRTH aktiv' team is conducting follow-up investigations on the first group of subjects in order to assess the trial's long-term value and influence. The scientists are monitoring whether, and the extent to which, the participants are continuing with exercise.

By Michael Ott, MD

Rubens revisited

Prometheus Bound, *begun c. 1611 to 12, completed by 1618. Peter Paul Rubens and Franz Snyders (Philadelphia Museum of Art, purchased with the W. P. Wilstach Fund), image courtesy of the Philadelphia Museum of Art*

Peter Paul Rubens' *Prometheus Bound* (begun in 1611–1612 and completed by 1618) is probably the work of art most cited in modern medical science to illustrate the 'regeneration' of the human body.

In June 2016, I had the privilege of attending a scientific meeting in Philadelphia. While waiting for my flight home, I decided to walk down Jefferson Avenue to the Philadelphia Museum of Art. In one of the museum's rear galleries, I found the original masterpiece with its dark colours and vivid portrayal of movement.

A divine punishment for an immortal hero

In Greek mythology, Prometheus was a Titan who stole a torch from Mount Olympus and brought fire to humanity. In turn, Zeus punished Prometheus by chaining him to a rock and commanding an eagle to devour a piece of his liver every night. The punishment was everlasting since the liver perpetually regenerated – truly a divine punishment for an immortal hero! The canvas not only tells us about the power of liver regeneration, but also provides lessons for all of us who work in contemporary science.

If you take a close look, you will see that the picture has subsequently been extended to the left. In the 17th century it became popular to do justice to the scenery and not merely focus on the drama. With this enlargement, one's eyes are now drawn to the beautiful landscape and the water on the far horizon. So, if you have a good look at your own work, your next manuscript in the field of modern regenerative science might already be a piece of art, but make sure you do your data justice and give them 'power' to tackle the worst maladies of humankind.

Tell the right story!

Another thing you might learn from this painting is to choose the right story for your data. The modern-day discipline of 'storytelling' was already in place in the 17th century, and Rubens was truly a master storyteller. Just 30 years earlier, Titian, another painter of the medieval age, captured the same subject matter, namely an eagle eating the liver of a hero. But the story was different, the punishment here being given by Zeus to his son Tityus, who sexually assaulted the goddess Letho. Rubens copied the subject, but he then told the vibrant and inspiring myth of Prometheus giving humankind the long-awaited gift of fire. You can see Prometheus fixing his gaze on the eagle and proudly enduring the pain. Four centuries later, the Rubens picture has become an artistic icon throughout the world and Titian's work has almost been forgotten. So be Rubens, *not* Titian, and the world of science will love you!

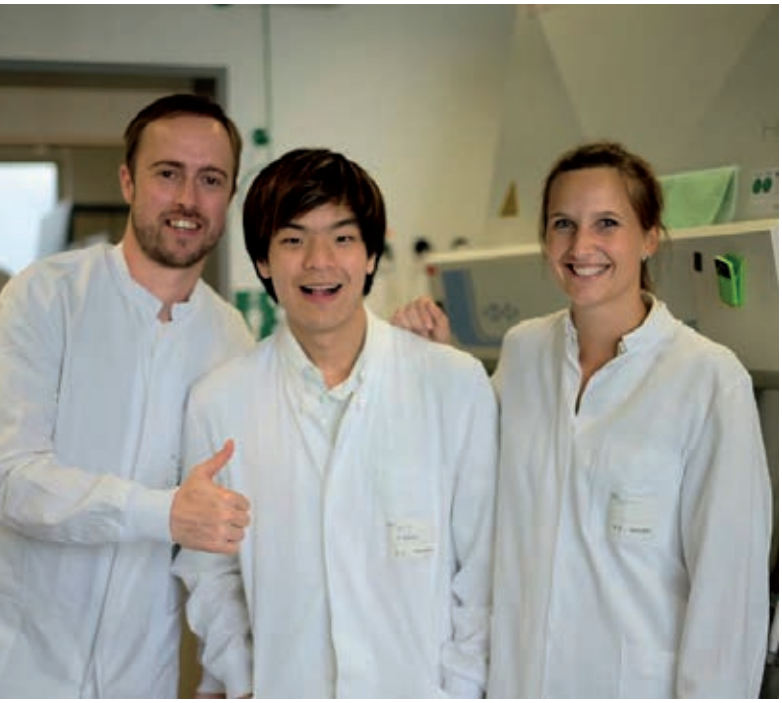
Be proud of your achievements!

Many famous medieval artists such as Leonardo da Vinci and Michelangelo, as well as Peter Paul Rubens, employed other artists in what might be called a 'painter´s laboratory'. Rubens, who was not at all good at painting animals, asked Frans Snyders to incorporate the eagle into the picture. Many other paintings attributed to Rubens were probably not created by him, but later finished and signed by the master. So, if you think you are a Frans Snyders of modern science, be proud of your contribution to a masterpiece and don´t forget to take the credit for it!

Repeat and refine!

I left the room and Ruben´s painting and headed to the museum's exit. On my way back I passed another famous painting, Vincent van Gogh's Sunflowers. Whereas Rubens was the darling of high society with his 'fleshy' style, van Gogh was lonely and struggled with psychiatric illness. Could modern science also learn something from this painter? Repeat and refine! Twelve sunflowers for Philadelphia, fifteen for London, fifteen for Amsterdam….

International exchange: medicine meets research



from left: Nico Lachmann, Chisanu Thumarat, Alexandra Kuhn

Standing Committee On Research Exchange (SCORE)

SCORE is a project organized by the International Federation of Medical Students' Associations (IFMSA), which places international medical students with different research organizations. The aim of this research exchange initiative is to give medical students from all over the world an inside look at research, and the chance to learn new techniques and establish collaborations.

http://ifmsa.org/research-exchanges/

"Our aim is to bring young scientists together with medical professionals or students of human medicine at an early stage so that potential therapeutic options we're developing in our lab can be translated into clinical use later on," says Dr Nico Lachmann, who heads the REBIRTH unit on Translational Hematology of Congenital Diseases. Against this background, it was Jenny Lam – a medical student at Hannover Medical School (MHH) and a former doctoral student in the REBIRTH unit on Reprogramming and Gene Therapy – who drew Dr Lachmann's attention to a programme entitled Standing Committee On Research Exchange (SCORE), which places international medical students with various research institutes worldwide. "We are always on the lookout for talented medical students who wish to broaden their horizons," adds Dr Lachmann. Indeed a good reason to announce a call for projects. And this was no sooner said than done!

"Working with international medical students is very rewarding!"

Chisanu Thumarat of Vajira Hospital at Navamindradhiraj University in Bangkok, Thailand, applied for a one-month project – and, in June, he came to MHH. He very much enjoyed his time at the University and in REBIRTH. "I would like to say a big thank-you for this opportunity. Within this really nice, friendly team, I've learned a great deal about research in general, research publications and organizations, and laboratory techniques, and the month just flew by," the budding medic commented on his final day in Hannover. Chisanu is already back in Bangkok, where he is reporting on his experience. And in Hannover, too, his temporary colleagues are still reflecting on this exchange visit: "It's very rewarding to work with international medical students like Chisanu, to compare notes and make new friendships," says Ph.D. student Alexandra Kuhn (of the REBIRTH units on Reprogramming and Gene Therapy / Translational Hematology of Congenital Diseases), who looked after him.

from left: Johann Bauersachs, Tibor Kempf

Six million euros in funding for clinical researchers

Good news: the German Research Foundation (DFG) is funding the new Clinical Research Unit 311 to the tune of more than six million euros over three years. This group will help patients with severe heart and lung conditions by optimizing treatment strategies that relieve the strain on these organs or functionally replace them. This can buy time to treat the underlying condition or wait for a donor organ.

"We want to enhance the mechanical relief experienced and also find new biological or pharmacological therapies that aid recovery of these organs. The aim is, in this way, to achieve lasting improvement to these patients' poor prognosis, to extend their lives and improve their quality of life," says Professor Johann Bauersachs. Bauersachs is the spokesperson of the Clinical Research Unit on '(Pre) terminal Heart and Lung Failure: Mechanical Relief and Repair', and head of Hannover Medical School's (MHH) Department of Cardiology and Angiology. His colleague Professor Tibor Kempf will head up this new research group.

Seven MHH departments and institutes are participating in this Clinical Research Unit, in which 11 projects are to be tackled:

- Department of Cardiology and Angiology
- Department of Pulmonology
- Department of Cardiac, Thoracic, Transplantation and Vascular Surgery
- Paediatric Cardiology and Intensive Care Medicine
- Department of Nuclear Medicine
- Institute of Molecular and Translational Therapy Strategies
- Institute of Diagnostic and Interventional Radiology

Implant development: new service for translation-related matters

The REBIRTH Cluster of Excellence participates in the Clinical Translation module of the 'Biofabrication for NIFE' research alliance. This means that REBIRTH researchers, too, can avail themselves of the advisory services of the module headed by REBIRTH coordinator Professor Haverich and Professor Lenarz (MHH).

from left: Anneke Loos, Esther Lipokatic-Takacs, Franziska Lexow, Andreas Kampmann, Henning Voigt

The staff on the Clinical Translation module support scientists seeking to move research findings into clinical application. This team advises researchers on matters relating to approval, product classification, and testing strategies subject to approval conditions. Another main focus is on advice and assistance for the introduction of quality-management systems, and the drawing-up of standard operating procedures (SOPs) or other documents relevant to quality management.

Training for scientists, medics and industry partners

This work group also organizes regular training for scientists, medics and industry partners, at which experts raise participants' awareness of issues related to translation. These matters include the regulatory environment for the approval of medical devices and tissue-engineered products, profitability considerations, and clinical trial procedures as part of the approval process, as well as quality-management aspects.

A contact point for higher-education research, hospitals, industry and public authorities

The team also initiates discussion with potential industry partners and public authorities, who play a vital role in the translation process involved in successfully developing and launching new implants. The module hopes to become a platform and point of first contact for ongoing dialogue between the higher-education research world, hospitals, industry and relevant authorities.

Biofabrication for NIFE

'Biofabrication for NIFE' is an interdisciplinary research alliance that develops novel, personalized implants. The three participating Hannover higher-education institutions are the city's Medical School (MHH), University (LUH) and University of Music, Drama and Media (HMTMH). Its focus is on improving patient safety and implant life. This research partnership has been funded by the federal state of Lower Saxony since 2013

Alongside services in the strict sense, the work group will also analyse the existing local set-up and the as-is situation in respect of translation within biofabrication-related projects. The aim here is to identify the current translation pathways as well as obstacles and potential for improvement. The initial findings of a representative study have already been published.

Contact: Dr Esther Lipokatic-Takacs & Dr. Franziska Lexow (Tel. +49 (0)511 532 7302 & 7303), www.biofabrication.info

Publication

Duda F, Lipokatic-Takacs E, Loos A, Lüdtke N, Wilhelmi M, Kampmann A, Voigt H, Schubert C, Elff M, Lenarz T, Haverich A. Institutional and sociopolitical factors in supporting clinical translation: the case of biomedical implant research in Hannover, Germany. BioNanoMat *2016, 17 (1-2): 89-92, https://www.degruyter.com/abstract/j/biomat.ahead-of-print/bnm-2015-0023/bnm-2015-0023.pdf*

A series of training sessions: 'Public authorities relevant to the translation process'

Since 2013, the Clinical Translation module has provided a series of training sessions for research and clinical staff on aspects of translation. As of September 2016, the new thematic focus is on optimizing communication with the public authorities involved in the approval process. The series will include an introduction to bodies such as the following: the Paul Ehrlich Institute (PEI), the commercial regulatory authority (*Gewerbeaufsichtsamt*) and the German Federal Institute for Drugs and Medical Devices (BfArM). Representatives of the organizations themselves will be invited to speak. These sessions are held every second Thursday in the month between 5 and 6 p.m. Events are announced via the REBIRTH mailing list.

from left: Nico Lachmann, Christine Happle

The Volkswagen Foundation will be your host on 1 November 2016 at 8.30 p.m.

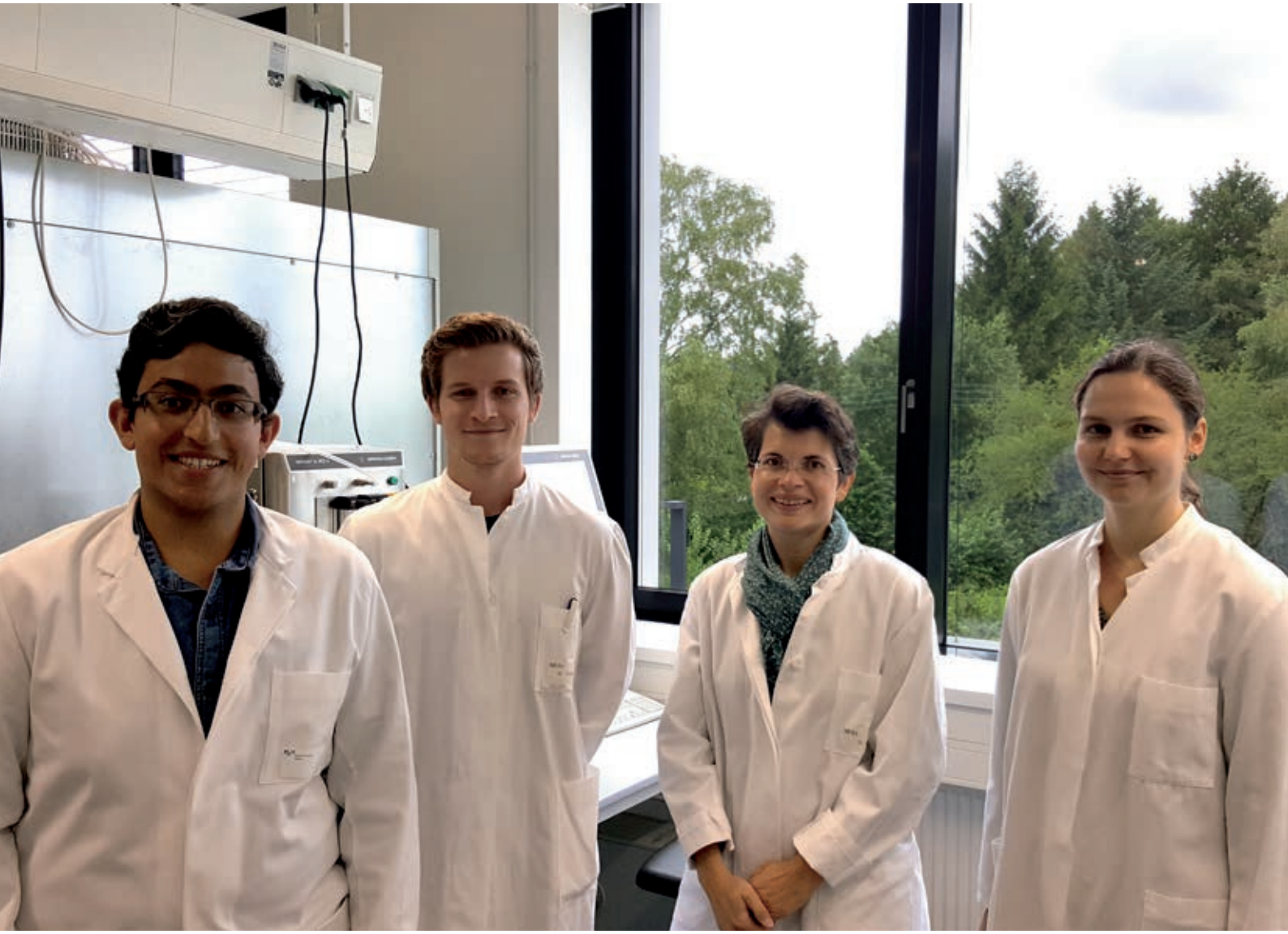
Stem cells = allrounder.

What is regenerative medicine able to do?

The dream of regenerative medicine is to make spare parts for the human body in the lab to save the lives of seriously ill people. This hope lies in the new allrounders of the cell world: induced pluripotent stem cells. They can already be used to produce blood cells that could one day make up for the shortfall in blood reserves. And that's not all: stem cells harbour considerable potential for new treatments, creating a real opportunity for medical breakthroughs. Human biologist Nico Lachmann and medic Christine Happle are working together to develop just such a therapy for sufferers of a rare lung disease.

The Volkswagen Foundation will be hosting an event, involving audience discussion, at which Lachmann and Happle will be looking at the possibilities and limits of stem cell research, the impact of these cells on medicine and why science fiction could soon become reality. The venue is Herrenhausen Palace, the forum is the *Herrenhausen Late* series of events, and the time is 8.30 p.m. on 1 November 2016.

www.volkswagenstiftung.de/veranstaltungskalender.html (in german)



from left: Naveen Rathi (exchange student), Niklas Jeinsen (PhD candidate), Ulrike Böer (team leader) und Skadi Lau (PhD student in the Ph.D. programme in Regenerative Sciences/supervisor of Naveen)

DAAD RISE Germany: Research Internships in Science and Engineering

RISE Germany is a programme supported by the German Academic Exchange Service (DAAD) to encourage international exchange in science and engineering. It enables Bachelor's students from Canada, the USA and the UK to do a 10- to 12-week internship at a higher-education institution or non-university research establishment, both improving their professional skills and gaining insight into German culture. During their stay they are looked after both professionally and personally by a doctoral student, enabling the latter to pass on their knowledge and acquire experience of guiding younger undergraduates.

In November 2015, the workgroup on Vascular Tissue Engineering, led by Dr Ulrike Böer and Professor Mathias Wilhelmi, applied to have a scholarship recipient by submitting a brief project description to the DAAD. Following the project's approval, undergraduates from Canada, the USA and the UK had the opportunity to apply for this and two other projects. By the January 2016 deadline, 21 candidates had applied for the project. They were then listed by the workgroups's preference, after which the DAAD compared these preferences with the applicants' own. Where successful matches were found, both parties were notified in March 2016 and planning for the internship entered the active phase. This involves the doctoral student helping the intern with various organizational aspects such as finding a hall of residence and opening a German bank account. The internship is funded either by a full DAAD scholarship or by a joint DAAD/institute scholarship. Under a full scholarship, the DAAD meets all costs. With a joint scholarship, DAAD provides health insurance, accident and personal-liability insurance, as well as travel costs for the three-day RISE meeting held in Heidelberg for all exchange students. The institute in question pays the monthly costs of €650 for accommodation and meals. This means that RISE participants need only meet travel costs to Germany and back to their home country.

Naveen Rathi (aged 20) is in his second year of a degree in Biomedical Engineering at the University of Utah, USA. Naveen, who received a joint scholarship from the DAAD and REBIRTH, spent his research internship (between 6 June and 5 August 2016) with the unit on Vascular Tissue Engineering at the Lower Saxony Centre for Biomedical Engineering, Implant Research and Development (NIFE). During this period he worked on a bioreactor system that enables blood vessels and stents to be incubated concurrently at different oxygen concentrations. Following successful preparation of medium conditioning, he cultivated various human, animal and artificial vessels that he then characterized using histological staining. In addition to his research work, he enriched the group culturally in many respects, as well as personally and linguistically.

Altogether, the DAAD's RISE Germany programme provides all those involved with an opportunity to learn from each other and to make contacts that greatly broaden their own horizons. The next round of applications starts in October 2016 – perhaps we've aroused someone's interest?

Proposed projects for 2017 ...

... can be submitted to the DAAD between 1 October and 15 November 2016.

More information is (only in german) available at: www.daad.de/rise/de/rise-germany/praktikum-anbieten/

The next newsletter will be issued at the end of December 2016.

upper row left to right: Anett Witthuhn, Steffi Liebhaber, Marwa Farid, Anamika Chatterjee, Marisa Granados-Pastor, Debapriya Saha, Hsin-Chieh Tsay.
lower row left to right: Rodrigo Rodriguez Jauregui, Adele Mucci, Akshay Menon, Stefan Kalies

Don't get lost in translation – better chill without regrets.

It was a large graduation ceremony on 10 June 2016: as many as 11 graduates of the Ph.D. programme in Regenerative Sciences received their doctoral certificate at the event held in a full lecture theatre (room H) at Hannover Medical School (MHH). Adele Mucci of Thomas Moritz' laboratory team also found out on this occasion that her publication had just been accepted by the journal *Stem Cell Reports*. The supervisors said a few personal words (illustrated accordingly) of congratulation to their Ph.D.-students. Graduation is, in many respects, a suitable opportunity for recalling times past: among the external assessors on this occasion were several MHH alumni whose career paths had taken them to other higher-education centres. They included Professor Ute Modlich from Frankfurt's Goethe University and Dr Hannes Klump of Essen University Hospital. This time it was not only the graduates (from six different countries: Egypt, Germany, India, Italy, Mexico and Taiwan) who were an international mix, but also those on the panel, among whose number were assessors who had travelled from the UK and the Republic of Ireland. Afterwards, many of the new postdocs packed their bags – some were going on holiday, others back to their home countries, and still others starting a new chapter in their lives. And, to wish them all well collectively, we'd like to borrow phrases from publications by some of our graduates: "Don't get lost in translation – you're better off chilling without regrets (1, 2)!"

1. Ackermann M, Liebhaber S, Klusmann JH, Lachmann N. Lost in translation: pluripotent stem cell-derived hematopoiesis. *EMBO Mol Med*. 2015;7(11):1388-402. doi: 10.15252/emmm.201505301.

2. Chatterjee A, Saha D, Glasmacher B, Hofmann N. Chilling without regrets: Deciphering the effects of cryopreservation on the epigenetic properties of frozen cells will benefit the applications of cryo-technology. *EMBO Rep*. 2016;17(3):292-5. doi: 10.15252/embr.201642069.

Regenerative Sciences PhD programme

Who is Who

***Mónika Szepes** (29) aus Ungarn, REBIRTH Unit 5.7 – Myocardial Tissue Engineering*

What are you working on and why?

In my work group we are aiming to create patient-specific prevascularized cardiac tissue patches for transplantation into the necrotic area in the patient's heart following myocardial infarction. We believe this approach would overcome the major recent problems in cardiovascular diseases, namely the shortage in transplantable donor organs and the lifelong immunosuppression of patients. Of course, there is a long way to go before clinical application. My contribution is to differentiate pericytes from human induced pluripotent stem cells (hiPSCs) and use them together with hiPSCs-derived endothelial cells for the vascularization of our tissue-engineered cardiac patches.

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

When I saw the advertisement for the Ph.D. programme, I thought it might be just the place I'm looking for. During my Master's thesis I worked with an *in vitro* model of cardiac ischemia and cell therapy, and when I was on Erasmus in Portugal I also gained some experience with biocompatible materials for regenerative science. While considering my options for the future, I dreamt about having those two fields (cell therapy and biomaterials) combined in my Ph.D. project and I felt very happy to be offered a place here involved with cardiac tissue engineering.

What do you like about science?

I have a curious nature, so I find it fascinating to work on problems that have not been solved yet. The interdisciplinary and international environment is very inspiring and I have the chance to use a wide range of advanced methods and techniques. I am driven by the hope that my research will bring some improvement in regenerative medicine.

Where do you call 'home'?

In everyday conversation it is context-dependent. Generally, I call my lovely apartment in Hannover 'home', and 'home home' is the term used for my home country, Hungary, or more precisely the house where I grew up in Budapest.

What do you do in your spare time?

Travelling is my absolute passion. Whenever I have the time and the opportunity I take my backpack and set off to discover new places. I am also an enthusiastic cook who enjoys trying different cuisines and bringing the taste of faraway countries into the kitchen.

Nico Lachmann

From student to supervisor

He was late joining the Ph.D. programme in Regenerative Sciences. At the time of the application interviews, Nico Lachmann was doing research for his Master's thesis in the USA – specifically, in the laboratory of Professor Richard Flavell at Yale University School of Medicine's Department of Immunobiology. So it wasn't until after his return from the States that he met with the Ph.D. Committee, and he was not enrolled in the class of 2008 until 20 October. For his doctorate he chose to work in the lab of Professor Thomas Moritz, who himself had not come to Hannover

Medical School (MHH) until July 2008 to assume the leadership of the REBIRTH work group on Reprogramming. This proved a match made in heaven: the two investigators have now jointly contributed to 21 publications, for nine of which Nico Lachmann is lead author and Professor Moritz senior author. After only three years, Dr Lachmann defended his thesis on 27 January 2012, one of the first of the 2008 intake to do so; it bore the title 'Strategies for Cell-Type Specific and Time Dependent Transgene Expression in Hematopoietic Gene Therapy'. For his postdoctoral research Dr Lachmann remained in Professor Moritz' lab, where he increasingly sought independence as a scientist in his own right. Since the summer of 2014 he has been a member of the inaugural year of the Young Academy, with which MHH supports the careers of the next generation of medics by providing human and material resources as well as a setting that encourages networking within the School. Since March 2015, Dr Lachmann had headed up his own research group, Translational Hematology of Congenital Diseases, which is funded by the REBIRTH Cluster of Excellence. Then, on 15 June 2016, he was awarded one of the highest academic accolades there is: the appropriate panel of the MHH Senate awarded Dr Lachmann the venia legendi in Regenerative Medicine for obtaining his Habilitation (postdoctoral lecturing qualification). July 2016 then saw the first publication with Nico Lachmann credited as (co-)senior author and, in October 2016, he will be the sole supervisor of two Ph.D. students from among the new intake on the Ph.D. programme in Regenerative Sciences. We congratulate him on 'graduating' from doctoral student to doctoral supervisor and are looking forward to working with him in his new role!

Curiosity – the engine driving innovation

The motivation to make new discoveries is the engine that drives innovation: all of the members of the new REBIRTH unit on Translational Hematology of Congenital Diseases, formed in March 2015 within the Institute of Experimental Hematology and the REBIRTH Cluster of Excellence, are passionate about science. The scientists and medics in this group are working together to develop new treatments for blood diseases. The aim is to combine established knowledge with new findings to bring about innovation. "By joining forces with other units within REBIRTH, we have established a new technique that allows us to produce mature blood cells on a large scale," says Dr Lachmann. The research group is currently exploring the use of these cells both for rare genetic conditions and for common infectious diseases. As well as its two scientists, Dr Nico Lachmann (who heads the unit) and Dr Mania Ackermann, the group also includes technician Theressa Buchegger, and medical student Jan Schiller who is currently completing his doctoral thesis. In October, two Ph.D. students from the Ph.D. programme in Regenerative Sciences will be strengthening the team.