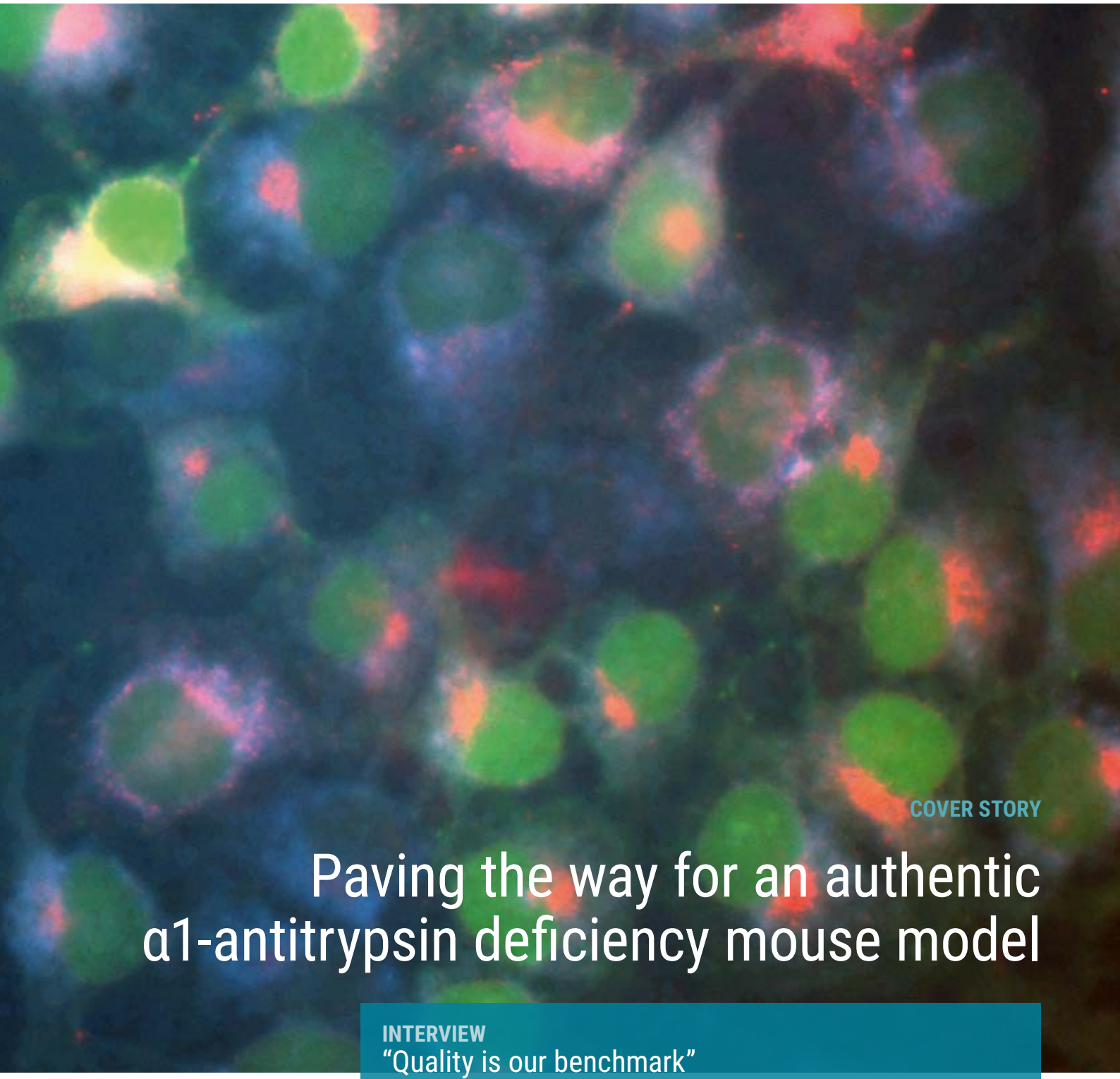
rebirth news 2 SEPTEMBER 2018



COVER STORY

Paving the way for an authentic α1-antitrypsin deficiency mouse model

Latest Publications

Ethical considerations on human-animal chimeras

The prospect of creating and using human-animal chimeras and hybrids (HACHs) that are significantly 'human-like' in their composition or behaviour has been suspected of conjuring up 'inexorable moral confusion'. This paper tries to show that this confusion may ultimately be grounded in a paradoxical intertwinement of two kinds of what are known as species arguments – namely 'individual species arguments' and 'group species arguments', which articulate opposing demands but are conceptually interdependent. As a consequence, the existence of HACHs may challenge precisely those normative standards on which the protection of these hybrids and chimeras may eventually be based.

Publication

Hübner D. Human-Animal Chimeras and Hybrids: An Ethical Paradox behind Moral Confusion? *J Med Philos*. 2018 Mar 13;43(2):187-210.

West syndrome: patient-specific hiPS model

In West syndrome sufferers, deficiency of the ST3GAL3 gene can lead to epilepsy and intellectual disability. REBIRTH researchers obtained fibroblasts from a patient with West syndrome and a healthy sibling, and used them to generate induced pluripotent stem (iPS) cells. They applied different techniques to analyse the cells and neurons derived from them. This revealed that changes in the sialylation pattern on the surface of specific neuronal cell types affected (adhesive) interactions between these cells and the surrounding environment. This may, they believe, impair the formation of neuronal structures during embryonic development, which is the cause of West syndrome.

Publication

van Diepen L, Buettner FFR, Hoffmann D, Thiesler CT, Halbach O, Halbach V, Jensen LR, Steinemann D, Edvardson S, Elpeleg O, Schambach A, Gerardy-Schahn R, Kuss AW. A patient-specific induced pluripotent stem cell model for West syndrome caused by ST3GAL3 deficiency. *Eur J Hum Genet*. 2018.

Scalable differentiation of hiPS into endothelial cells

Endothelial cells (ECs) are an integral part of vascular structures and the vascular system. These cells, which have a wide range of functions, are used in cellular therapies and are important components of engineered tissue constructs and *in vitro* disease models. ECs can be isolated from various primary sources, although this is subject to limitations in terms of quantity and quality. This paper describes how, as an alternative, REBIRTH researchers developed an approach by which human induced pluripotent stem cells (hiPSCs) can be differentiated into endothelial cells in scalable suspension culture. The protocol established here allows the generation of ECs in relevant quantities for future regenerative approaches.

Publication

Olmer R, Engels L, Usman A, Menke S, Malik MNH, Pessler F, Göhring G, Bornhorst D, Bolten S, Abdelilah-Seyfried S, Scheper T, Kempf H, Zweigerdt R, Martin U. Differentiation of Human Pluripotent Stem Cells into Functional Endothelial Cells in Scalable Suspension Culture. *Stem Cell Reports*. 2018;10(5):1657-72.

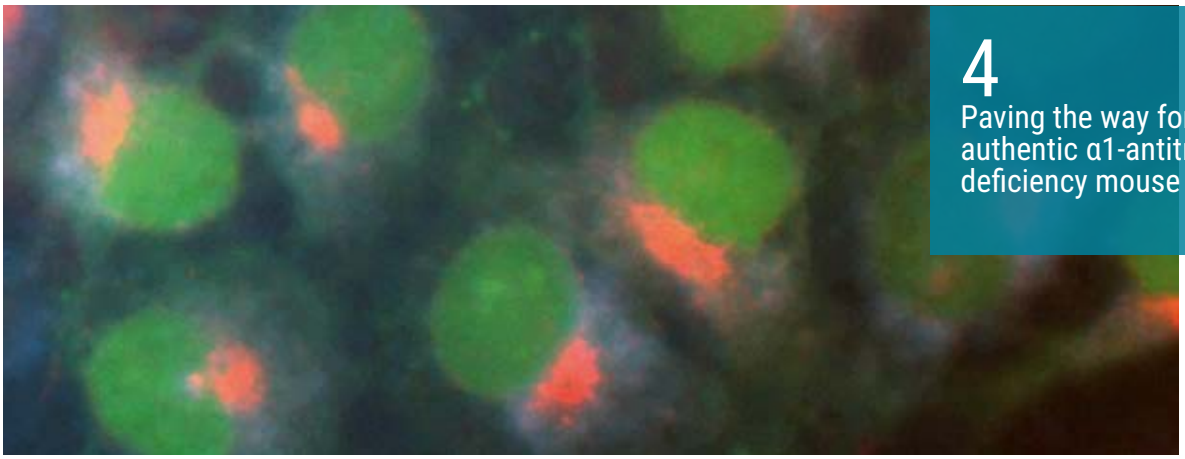
Polarity signalling coordinates remodelling of heart tube

The cellular mechanisms underlying the formation of the chambers of the heart remain largely unclear. In this paper, REBIRTH researchers show that the arrangement of cardiac muscle cells is a factor in the remodelling of these chambers. The planar cell polarity (PCP) signalling pathway is instrumental here. It determines in which regions of the (embryonic) heart tube the actomyosin cytoskeleton is particularly active. In turn, this actomyosin activity influences where the heart's muscle cells are redistributed, thus contributing to formation of the organ's chambers.

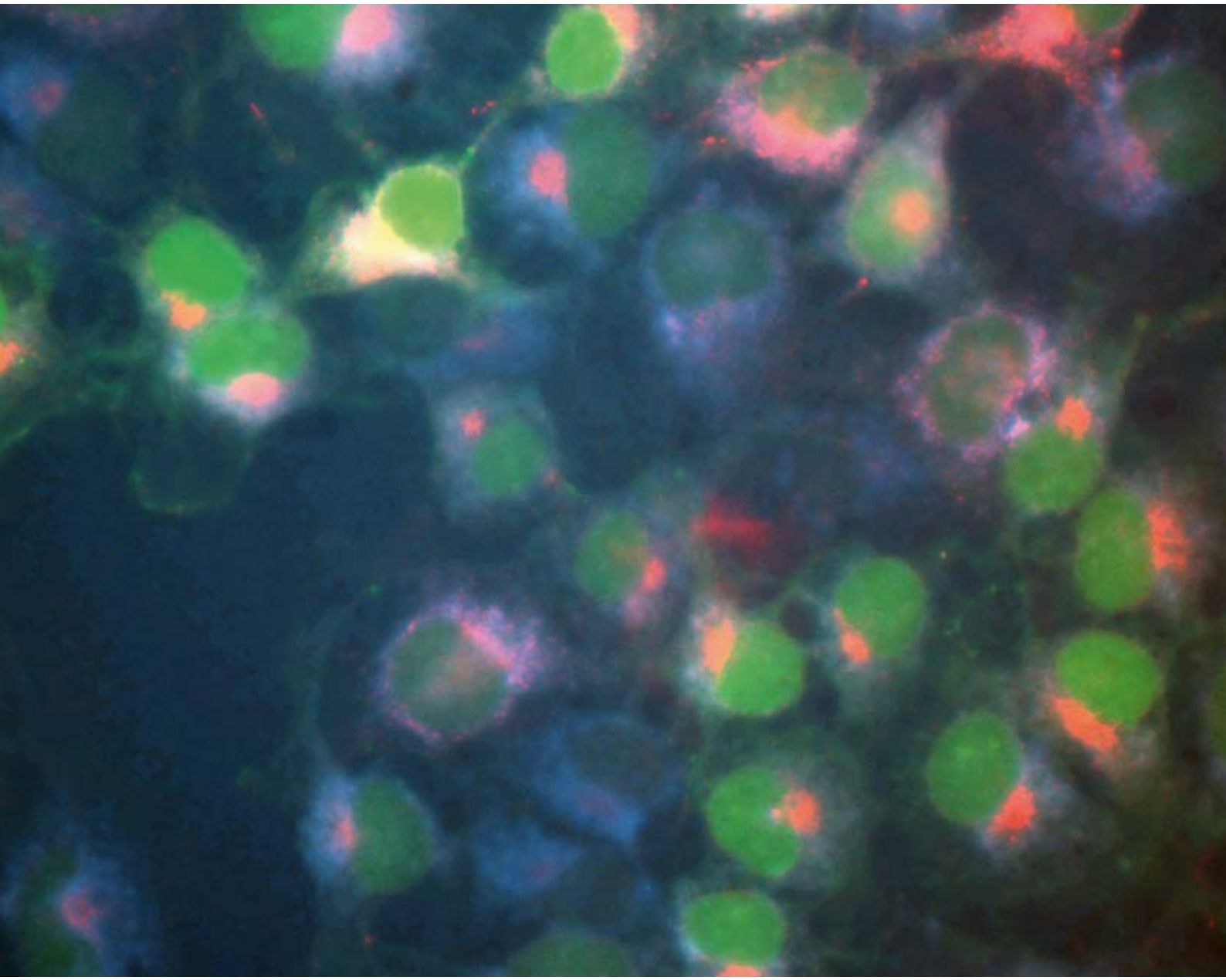
Publication

Merks AM, Swinarski M, Meyer AM, Muller NV, Ozcan I, Donat S, Burger A, Gilbert S, Mosimann C, Abdelilah-Seyfried S, Panakova D. Planar cell polarity signalling coordinates heart tube remodelling through tissue-scale polarisation of actomyosin activity. *Nat Commun*. 2018;9(1):2161.

Contents

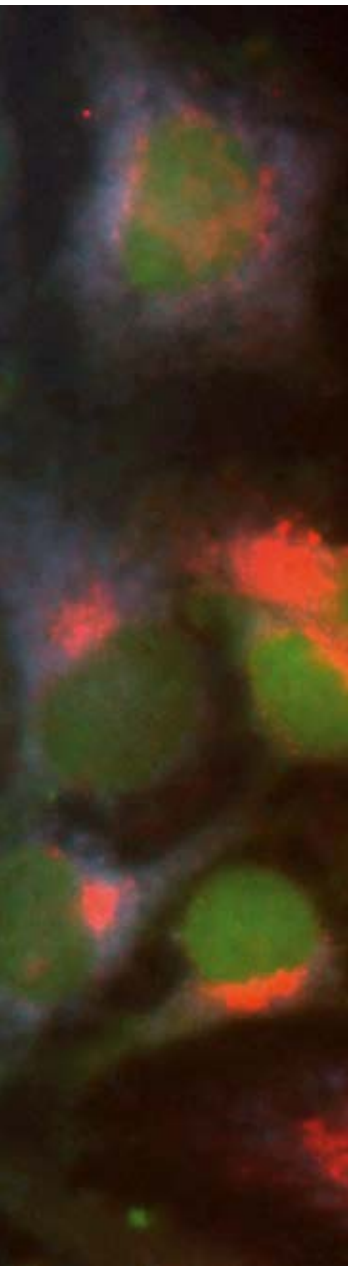


Paving the way for an authentic α1-antitrypsin deficiency mouse model



Immunofluorescence analysis of COS-7 African green monkey kidney cells expressing the mouse SERPINA1 paralogue DOM-7 (red: DOM-7; blue: endoplasmic reticulum marker Grp78/BiP; green: eGFP). The murine SERPINA1 genes are the orthologues to human α1-antitrypsin (SERPINA1) and they are important targets for the creation of authentic mouse models recapitulating human severe α1-antitrypsin deficiency.

Severe α1-antitrypsin deficiency (A1AT-D) is a rare congenital condition in which affected individuals suffer, to various extents, from lung and liver disorders caused by mutations of the SERPINA1 gene. These mutations lead to formation of chains called multimers and to retention of A1AT-D in the endoplasmic reticulum (ER) of the liver cells (hepatocytes) that produce it. As the cells are unable to secrete this important antiproteinase into the serum, this results in a deficiency of it there. In especially severe cases, patients suffer from chronic obstructive pulmonary disorder (COPD) or can develop carcinomas of the liver. At present, the extent to which additional environmental and genetic modifiers affect the course of the disease has been insufficiently investigated.



"A full A1AT-D mouse model would allow the investigation of extended disease mechanisms and testing of novel treatment options," says Dr Reto Eggenschwiler (REBIRTH unit on Translational Hepatology and Stem Cell Biology). "However, the generation of such models has been hampered by the high complexity of the mouse SERPINA1 gene locus." In mice, the SERPINA1 locus encodes for three to five out of seven known SERPINA1 paralogues. (Paralogues arise through multiple duplication of gene segments). The abundancy and expression of these paralogues is dependent on the exact mouse strain. Preparatory to creation of an A1AT-D mouse model using CRISPR technology, Dr Eggenschwiler has now – and for the first time – functionally characterized DOM-7, one of the seven SERPINA1 genes in mice.

DOM-7 is an inhibitor of neutrophil elastase and chymotrypsin

Some of the most widely used mouse strains – such as the BALB/cAnnCrl and FvB/N strains derived from Swiss mice,– express the DOM-7 gene. Thus far, however, it has been unclear what the exact function of this gene was. In a collaborative effort with the research team headed by Professor Jörn Stitz at TH Köln, Dr Eggenschwiler and Professor Tobias Cantz (leader of the REBIRTH unit on Translational Hepatology and Stem Cell Biology) have analysed the exact function of DOM-7. They found that this gene has the potential to inhibit both neutrophil elastase and chymotrypsin enzymes. "In patients with lung disease caused by severe α1-antitrypsin deficiency, neutrophil elastase is insufficiently inhibited. This is related to the breakdown of elastin fibre in the lungs, which results in COPD," Dr Eggenschwiler explains. "Therefore, DOM-7 must be factored in when seeking to generate functional A1AT-D mouse models from DOM-7-positive mouse strains by gene knockout."

> *"A full A1AT-D mouse model would allow the investigation of extended disease mechanisms and testing of novel treatment options."*

This work was supported by the German Research Foundation (DFG), through the REBIRTH Cluster of Excellence (DFG EXC 62/3) and the collaborative research centre 'Optimization of Conventional and Innovative Transplants' (SFB 738). Reto Eggenschwiler received support from Hannover Medical School (MHH) via the HiLF in-house funding scheme.

Publication

Jülicher K, Wähner A, Haase K, Barbour KW, Berger FG, Wiehlmann L, Davenport C, Schuster-Gossler K, Stitz J, Cantz T, Eggenschwiler R. Functional characterization of the mouse Serpina1 paralog DOM-7. Biol Chem. *2018;399(6):577-82.*

This image, created by graphic designer Kat Menschik, shows a cerebral cavernous malformation (berry) in a dense carpet of medicinal-herb flowers. Some of the active ingredients identified are obtained from these plants. The zebrafish in the picture represent the animal models used.

REBIRTH researchers identify potential drug to treat rare condition

Cavernous malformation of the brain: indirubin-3'-monoxime can relieve symptoms

A substance has been identified that alleviates symptoms of a rare vascular disease called cerebral cavernous malformation (CCM). It was found thanks to comprehensive analysis – using a mouse model – within a consortium headed by a researcher at Hannover Medical School (MHH) and the University of Potsdam (UP). In CCM sufferers, malformations of cerebral blood vessels may lead to brain haemorrhage and strokes. The scientists screened pharmaceuticals already approved for use in humans. Other members of the consortium include the Hospital for Sick Chil-

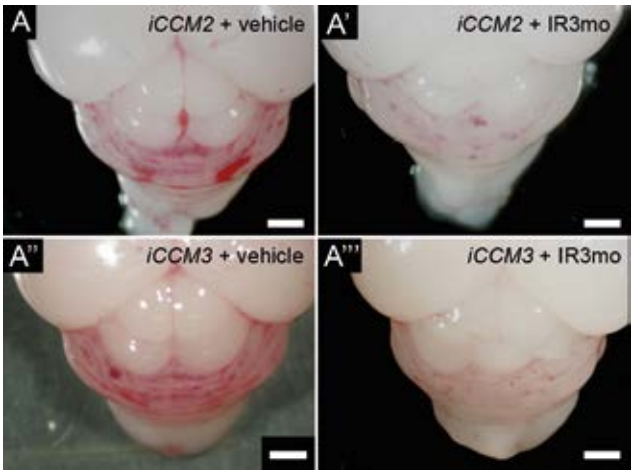
Cerebral cavernous malformation (CCM)

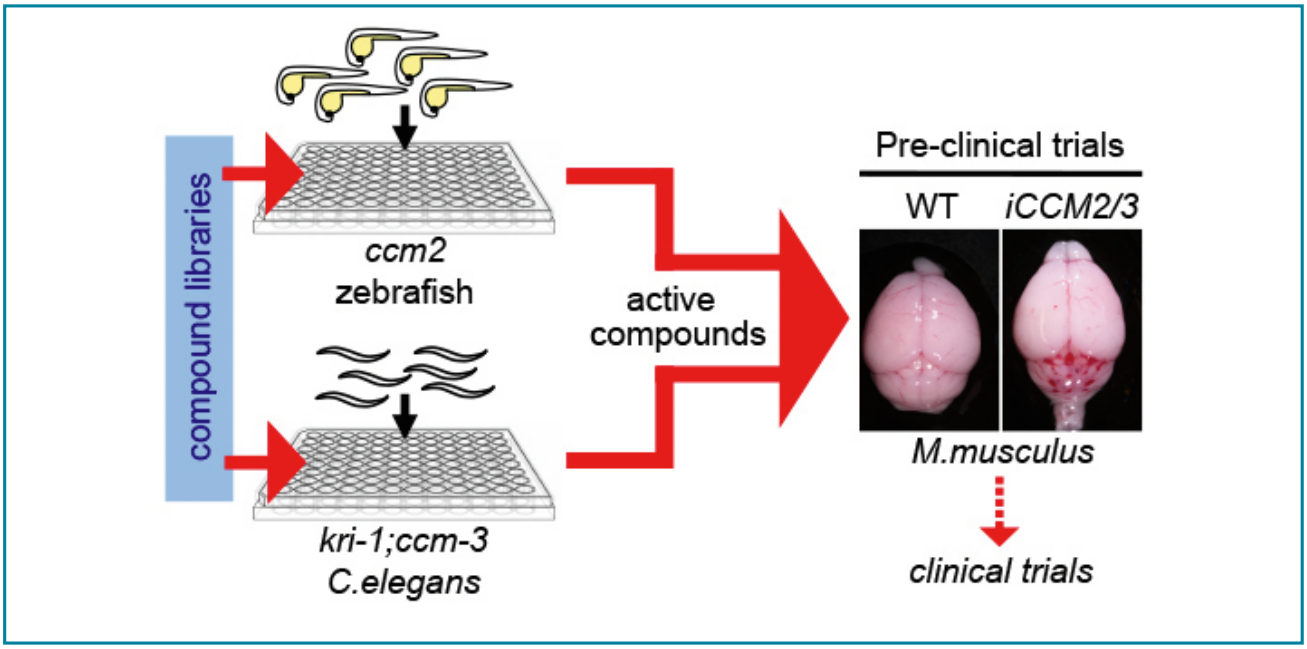
CCM is a relatively frequent condition that may occur in 0.5% of the population. The disease is generally not hereditary. However, these malformations in the brain may (in some cases) occur due to inherited mutations of three genes CCM1, CCM2 or CCM3). This familial form of the condition is very rare, with only one individual in 3,000 affected. The scientists believe early onset and severe progression of the disease are, in particular, associated with the mutation in the CCM3 gene.

dren (SickKids) in Toronto, Canada, the Université Paris Diderot and INSERM at Grenoble, France, as well as the Berlin-based *Leibniz-Forschungsinstitut für Molekulare Pharmakologie* (FMP). "At present, the only treatment option for this condition is a neurosurgical procedure, although this is possible only if the malformations are not too deep inside the brain and not in parts of the brain essential for survival," explains Professor Salim Seyfried, who is jointly appointed by UP and MHH. He is coordinating the study, which is being conducted by a transnational consortium (part of the E-RARE network) called CCMCURE. "There is an acute need for a medicine to treat this disease. In such a case, screenings of this kind – in which already existing drugs are analysed for potentially new uses – are the quickest way of finding one." The international team published its findings in the periodical EMBO Molecular Medicine.

The EU-funded consortium tested more than 5,000 compounds approved by the US Federal Food and Drug Administration (FDA) using established model systems for CCM, including nematodes, zebrafish eggs and (in humans) vascular wall cells. "The pharmaceuticals identified have allowed us to discover the relevant molecular signalling pathways and networks that may play a part in this condition. Analysing the molecular networks involved in CCM will also help in the development of combinatorial approaches to tackling this disease," says MHH professor Seyfried, head of REBIRTH unit on Zebrafish Cardiovascular Developmental Genetics. Additionally, some of the compounds identified in the analysis are candidates for treating other conditions of molecular origin.

This figure shows representative images illustrating the treatment of two different mouse models with indirubin-3'-monoxime. Left: control. Right: treated mouse strains.





This figure shows the overall experimental design.

Indirubin-3'-monoxime identified as a potential drug

Drawing on the outcome of analyses using animal models and human cells, the scientists began by investigating the

CCMCURE consortium meets

In July, the consortium members came together at the invitation of Professor Brent Derry (Hospital for Sick Children (SickKids) in Toronto) and Professor Peter Roy (University of Toronto) in the Canadian city. During their time together, the researchers took part in an information event held by the Angioma Alliance, an organization created by people affected by CCM, which is highly active in the USA and Canada. Consortium members Professor Elisabeth Tournier-Lasserve (head of the Molecular Genetics Laboratory at Lariboisière Hospital and director of INSERM unit U740 (Genetics of Vascular Diseases)), and Professor Salim Seyfried presented the findings of their joint study with CCM patients, after which they held a Q and A session.

effect of indirubin-3'-monoxime in mice. Indirubin-3'-monoxime is a pharmaceutical with only mild side-effects that is used in traditional Chinese medicine, where it is frequently chosen to treat leukaemia and other chronic diseases. In molecular and functional studies, the researchers had already discovered that indirubin-3'-monoxime prevents these malformations in human vascular cells and in zebrafish eggs. Their investigations using a mouse model revealed that 'feeding' juveniles with indirubin-3'-monoxime reduced the impact of the malformations.

Alongside the EU (the study's chief funder), the REBIRTH Cluster of Excellence also financially assisted the project.

Publication

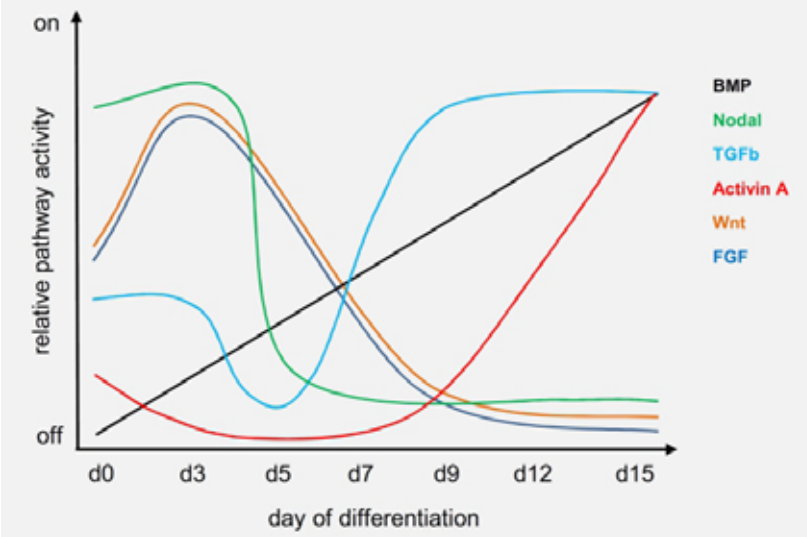
Otten C, Knox J, Boulday G, Eymery M, Haniszewski M, Neuenschwander M, Radetzki S, Vogt I, Hahn K, De Luca C, Cardoso C, Hamad S, Igual Gil C, Roy P, Albiges-Rizo C, Faurobert E, von Kries JP, Campillos M, Tournier-Lasserve E, Derry WB, Abdelilah-Seyfried S. Systematic pharmacological screens uncover novel pathways involved in cerebral cavernous malformations. EMBO Mol Med. *2018.*

Cardiac differentiation: which proteins do cells secrete?

Scientists can cause human pluripotent stem cells to differentiate into heart muscle cells (cardiomyocytes) in the lab, but the molecular processes involved are not yet fully known. So far, investigators have focused on proteins in the cell or cell membrane; they have paid little attention to those that, in tissues, control intercellular communication. Signalling molecules that play a role in morphogenesis during the development of multicellular organisms have proven especially hard for researchers to identify. One reason is the methodology used: researchers employ mass spectrometry to analyse the proteins in cell culture supernatants. (This term refers to the differentiation medium that contains high levels of albumin, which impedes identification of the signalling proteins – whose concentration is millions of times lower – in the measurement process.)

The team led by Falk Büttner, an adjunct professor who heads the REBIRTH unit on Stem Cell Glycomics and Proteomics, is joining forces with Dr Robert Zweigerdt (REBIRTH unit on Mass Production of Pluripotent Stem Cells and Derivates) to develop a means of albumin-free differentiation of pluripotent stem cells into cardiomyocytes. For this purpose, the team is itself using a medium supplement called B-27, which is employed in a wide range of differentiation media. In this way, they can make individual changes based on the original formula and, as was the case here, omit the albumin. "Commercially available

The figure illustrates the activity of different signalling pathways during the differentiation of human pluripotent stem cells into cardiac muscle cells, based on how many identified signal molecules there are in cell culture supernatants.



albumin is generally purified from bovine serum, and many people are unaware that this albumin is 'contaminated' by numerous other proteins, making it a completely undefined component for the medium," explains Professor Büttner.

Use of albumin-free B-27 enabled Dr Hanna Wolling – of the REBIRTH unit on Stem Cell Glycomics and Proteomics, and an alumna of the Ph.D. programme in Regenerative Sciences – to more precisely analyse the proteins secreted into the differentiation medium during the cell differentiation process. She did so at seven different time points, identifying more than 1,000 proteins, including many factors that modulate key metabolic signalling pathways. "Our results will contribute to a better grasp of the molecular mechanisms during cardiac differentiation," says Professor Büttner, supervisor of Dr Wolling, who defended her Ph.D. thesis in January 2018 and now holds a private-sector post as Technical Consultant for Chromatography in Aschaffenburg, Germany. It is for tissue engineering that these findings have the greatest potential: the signalling pathways could provide insights into the formation of heart tissue and necessary component structures such as connective tissue and blood vessels.

Publication

Wolling H, Konze SA, Hofer A, Erdmann J, Pich A, Zweigerdt R, Buettner FFR. Quantitative Secretomics Reveals Extrinsic Signals Involved in Human Pluripotent Stem Cell Cardiomyogenesis. Proteomics. 2018 Jul;18(14):e1800102.

About this publication

Issue no. 2, September 2018

Published by
REBIRTH Cluster of Excellence
Carl-Neuberg-Straße 1
30625 Hannover
Tel.: +49 (0)511 532 6793
Fax: +49 (0)511 532 5205
www.rebirth-hannover.de

Design and editing:
Camilla Mosel, Tilman Fabian (responsible under German press law)
E-mail: mosel.camilla@mh-hannover.de

Overall layout & typesetting:
D. Kleimenhagen

Credits

S. 6: Kat Menschik
S. 11, 13, 14, 22: MHH/Kaiser
S. 17: Bodo Koltermann
S. 18: Jan-Rasmus Lippels/frische-fotografie.de

All other pictures REBIRTH

Subscription

Subscription
via e-mail to:
rebirth.sekretariat@mh-hannover.de

MHH is Germany's largest transplantation facility; indeed, it is among the world leaders in lung transplants. The MHH is to establish a new Transplantation Centre as one of the three pillars of the Centre for Organ Regeneration and Replacement (CORE 100).

An interview with Professor Axel Haverich.

„Quality is our benchmark"

Hannover Medical School (MHH) is creating a new Transplantation Centre. How will patients benefit?
All clinical departments at MHH that are involved with transplants will work closely together in the new Transplantation Centre. Experts in different organ systems will be able to communicate in depth. And many aspects that have hitherto been dealt with individually in the various departments will be brought into alignment.

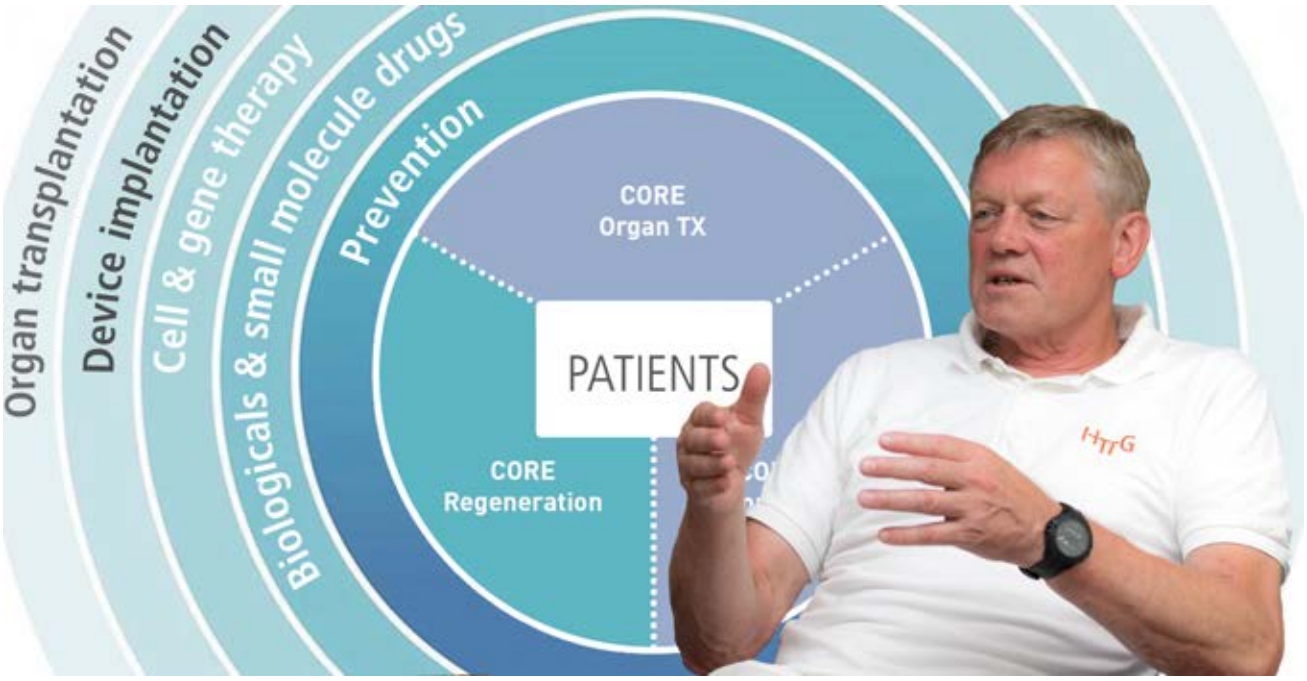
Organization of organ donation, waiting lists and organ allocation will be centrally managed, as will documentation of patient data. There will also be joint quality assurance, and harmonized aftercare models. All of these structural changes have a single goal: the best possible individual therapy for our patients with organ failure. They will benefit from the new Transplantation Centre because they can expect even higher quality across all levels of care.

Does a similar centre already exist elsewhere in Germany?
No, not yet. But the need is self-evident. So the Transplantation Centre at MHH will act as a model for others to follow.

Why is MHH ideal for this purpose?
MHH is among the forerunners in the field of transplantation. The very first kidney transplant here was back in 1968; its first liver procedure came in 1972, its first heart transplant followed in 1983 and the first lung procedure in 1988. And the School is also a pioneer in multi-organ transplants. MHH is home to decades of experience and to wide-ranging expertise concentrated in one place. Today it is the country's biggest transplantation facility. Which hospital could be more suitable as the site of a new Transplantation Centre?

The Transplantation Centre will be the successor facility to the Integrated Research and Treatment Centre Transplantation (IFB-Tx).
What will you take from the IFB-Tx?
The Transplantation Centre represents a perpetuation of the work of the IFB-Tx. For example, the IFB-Tx's quality-management activities will continue, as will those of the internal Scientific Advisory Board, which will coordinate and organize the scientific work. Also really important is the continuation of the Clinician Scientist Programme that advances the careers of junior researchers.

The ultimate measure of the Transplantion Centre's success will be the treatment outcomes there.
Will the patients also be structurally integrated?
Yes, they will. Germany's Federal Association of Organ Transplant Recipients (BDO) will have a representative on the external advisory board. It is of fundamental importance to us that patients are also stakeholders.



What work-related changes will the new Transplantation Centre bring for the physicians of the clinical departments involved?

The new guidelines alone will make their job description easier. The closer proximity to colleagues from other departments that perform transplants will give greater scope for coordination between them. It will also considerably broaden their view of transplantation medicine, and they can deepen their knowledge.

When will the new Centre open and what will it cost?

The Centre's creation will be stepwise in nature. It should be completed by mid-2019. As to the costs, these will be met by MHH.

Are you hoping that the new Centre will mean higher patient numbers?

Patient numbers are not the be-all and end-all; what counts is the quality of the care we deliver. Quite apart from that, patient numbers cannot be increased just like that, because there are still too few organs being donated.

Transplantation medicine is continuing to advance. Are there already plans that extend beyond the new Centre?

Yes, there are plans for a Centre for Organ Regeneration and Replacement, to be called CORE 100. This will integrate the new Transplantation Centre with the REBIRTH Cluster of Excellence (From REgenerative BIology to Reconstructive THerapy) and NIFE, the Lower Saxony Centre for Biomedical Engineering, Implant Research and Development. Then, under the umbrella of CORE 100, the use of the best therapies from surgical, conservative and regenerative medicine, organ replacement and transplantation will be coordinated. All of this will be augmented by preventive and aftercare programmes. CORE 100 will, then, be a place where people affected by organ failure can receive comprehensive care, and for every stage of their condition – from very early on when transplantation is not yet even being considered, to the transplant itself and taking in the rest of their lives afterwards.

This is an edited transcript of the interview. The conversation in full length can be found (in German) in MHH Info 3/2018:
https://www.mh-hannover.de/fileadmin/mhh/download/ueberblick_service/Info_18.03/_10-03_MHHinfo-gesamt.pdf

Research translation – REBIRTH goes business

The social value of new medical findings is based on their translation into beneficial treatments, diagnostic procedures and functional preventive measures. Research translation therefore represents the future and is high on the agenda of the REBIRTH Cluster of Excellence. To this end, REBIRTH works with Ascenion GmbH – a company specializing in patenting and technology transfer – as well as local business-development enterprise hannoverimpuls GmbH and Leibniz Universität Hannover's (LUH) start-up consultancy, called 'Starting Business'. Together, these partners are establishing a programme that actively supports REBIRTH scientists in creating start-ups and in other activities related to commercializing research.

Hannoverimpuls GmbH has long experience in giving new firms a leg up. It helps them request start-up funding and with drawing up business plans and business models. Seminars are also planned, as are individual consultations covering all aspects of start-up life and commercial exploitation. There are long-term plans for Hannover Medical School (MHH) and NIFE to have their own 'ideas scout' to complement the work of 'Starting Business' at LUH. The intention is to support medical- and diagnostic-research spin-offs within the life sciences sector in an even more targeted way.

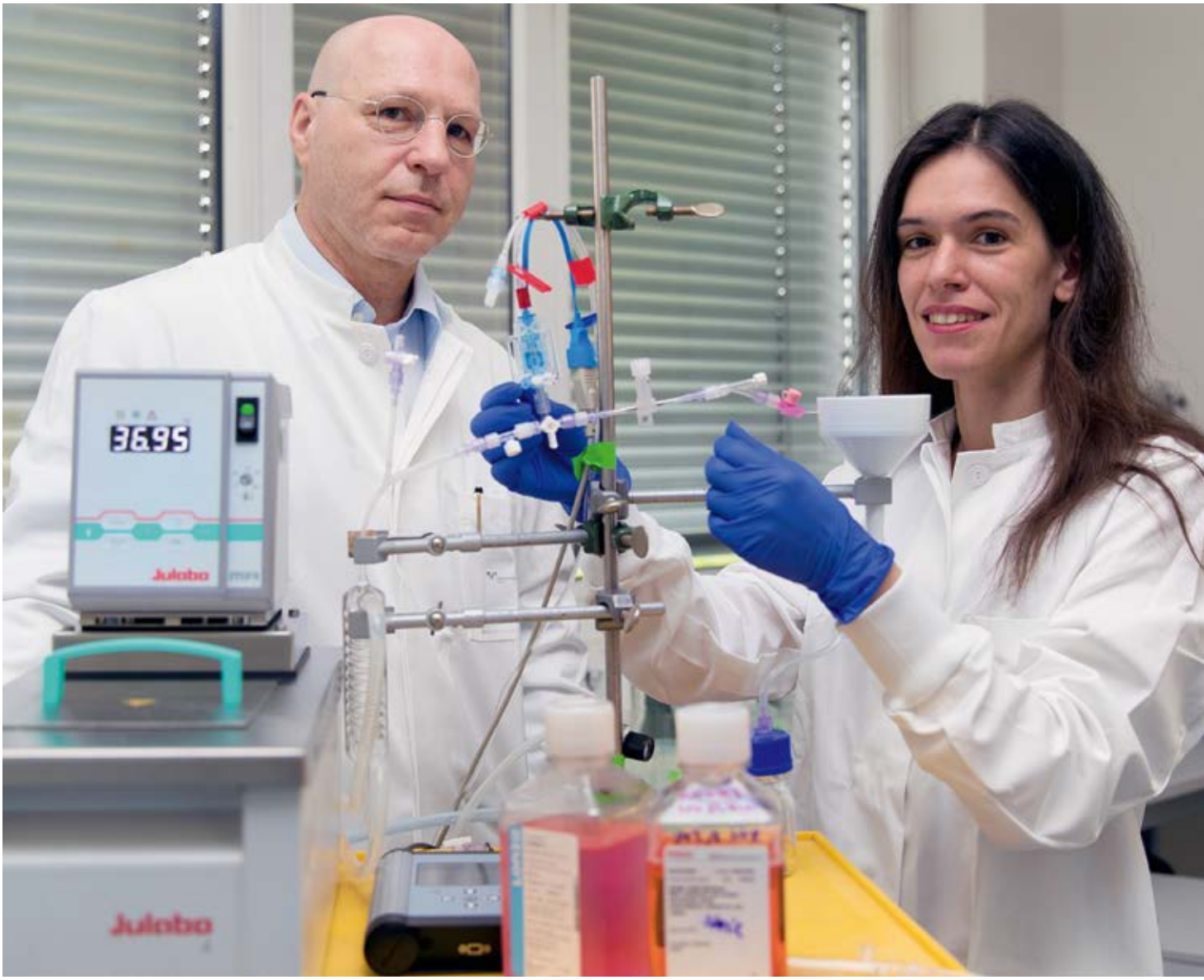
In recent months, initial services within this area have been trialled and have yielded positive feedback from the various REBIRTH units. Drawing on this experience, the programme will be expanded in a needs-driven manner. The REBIRTH management team will be happy to receive input about what people want it to include.

Contact: Lisa Braukmann
Email: Braukmann.lisa@mh-hannover.de

Hannover-based researchers seek to create 'invisible' organs

The recipient of a donor organ has embarked on a new chapter in their life with, say, a new, healty heart or liver. But they also live with the risk that their body will reject the transplanted organ. For example, this happens within the first five years to a quarter of those who have kidney transplants – despite being on medication to suppress the immune system. A team of scientists led by Professor Rainer Blasczyk of the Institute for Transfusion Medicine (ITM) at Hannover Medical School (MHH) now want to use a completely new strategy to prevent organ rejection and, more than this, to obviate the need for immunosuppression, which often has serious side effects such as infections or tumours. To this end, they are genetically modifying the donated organs so that the recipient's immune system does not detect them and hence does not reject them. MHH has teamed up with Hannover University of Applied Sciences and Arts (Professor Jens Hofschulte) and Leibniz Universität Hannover (LUH; Dr Jan Zeidler) to form a research alliance that will be funded for three years by the Lower Saxony Ministry of Science and Culture (MWK) to the tune of more than 1.2m euros. These funds are sourced from the European Regional Development Fund (ERDF) and federal-state resources.

The immune system recognizes a 'foreign', transplanted organ by its characteristic tissue markers. The researchers are now aiming to remove these cell structures by means of genetic engineering. Not only are they devising a technique to achieve this, they are also developing a special organ preservation system that allows *ex vivo* organ modification. After this, the organ is ready to be transplanted



Professor Rainer Blasczyk and Dr Constanca Sofia Ferreira de Figueiredo of the REBIRTH unit on Tolerogenic Cell Therapy.

into the recipient, whose immune system is no longer able to recognize its origin – it is effectively invisible.

The researchers on this project are using pig kidneys and a minipig animal model to conduct these experiments, preparatory to a follow-up study in humans planned to start in 2021. The intention is to then apply the technique in patients, at an MHH facility called the Organ Care Centre Hannover which will have been built by then – and not only for the kidney but also for other organs such as the lung, heart and liver.

As part of the current collaborative research project, the Institute for Risk and Isurance (IBVL) is also considering wider economic aspects, this being important in terms of whether health insurers may meet the costs at some point in the future. The researchers are also analysing whether this new technique is suitable for use with already immunized patients.

Horizon 2020: EU funding for REBIRTH

Imaging laboratories at MHH

MgSafe – postgraduate education

Biomedical imaging is one of the foundations of diagnostic analysis and treatment monitoring. The REBIRTH unit on Small Animal MRI is part of an Horizon 2020 Marie Skłodowska-Curie Innovative Training Network (called MgSafe) whose focus is on imaging of biodegradable magnesium-based implants. The project, coordinated by the *Helmholtz-Zentrum Geesthacht* Centre for Materials and Coastal Research (HZG), is receiving overall EU funding of 3.9 m euros. On 1 October, 15 aspiring pre-doctoral researchers start their training in the field of imaging and implantation technology at universities, research institutes and private companies in Austria, Germany, Italy, the Netherlands, Norway, Poland, Sweden and Switzerland. Dr Martin Meier, who heads this REBIRTH unit, will be guiding a Ph.D. student in his lab on the topic of 'Imaging of soft tissue remodelling and inflammation', for which he is being supported under the programme to the tune of 253,000 euros. Within the imaging division of Hannover Medical School's (MHH) Institute for Laboratory Animal Science and Central Animal Facility, another four doctoral students will receive further training through the programme.

The combination of state-of-the-art imaging techniques employed in this project.

V.A. Cure – postgraduate education

The REBIRTH unit on Zebrafish Cardiovascular Developmental Genetics has, together with seven European partners and five companies, received funding of almost 3.8 m euros for a H2020 Marie Skłodowska-Curie Innovative Training Network called V.A. Cure. The aim of this network is to train Ph.D. students as junior researchers in the field

of vascular biology, and to discover disease-causing mechanisms in order to develop new therapeutic strategies for vascular anomalies.

The 14 Ph.D. students in this network will be doing their research in universities, research institutes and private companies in Belgium, France, Germany, Sweden and Finland, starting on 1 March 2019. Under the programme, Professor Salim Seyfried, who leads the REBIRTH unit, will receive 498.000 euros over a three-year period to provide initial training to two of these students in his lab.

from left: Professor Ion Tighineanu, coordinator of NanoMedTwin, with Professor Axel Haverich, head of the MHH-Department of Cardiothoracic, Transplantation and Vascular Surgery.

CardioRNA: improving research integration

The REBIRTH unit on miRNA in Myocardial Regeneration, led by Professor Thomas Thum, has joined the COST Action CA17129 entitled 'Catalysing transcriptomics research in cardiovascular disease (CardioRNA)'. Professor Thum, also director of the Institute of Molecular and Translational Therapeutic Strategies (IMTTS), has been nominated as Substitute Member of the Management Committee on behalf of Germany. COST (European Cooperation in Science and Technology) actions are a European instrument to support cross-linking of national research activities at European level. COST actions do not support individual research projects; rather, they further networking activities such as conferences and exchange arrangements involving scientists. The main aim and objective of the COST Action CardioRNA is to accelerate the understanding of transcriptomics in cardiovascular disease and further the translation of experimental data into practical applications for diagnostics and therapies. This COST Action will be implemented for an initial period of four years, starting upon the first meeting of the Management Committee in October 2018.

Link: http://www.cost.eu/COST_Actions/ca/CA17129

Strengthening science and innovation

The EU is funding NanoMedTwin, a capacity-building measure, to the tune of just under 1m euros. Of this, almost 115,000 euros will be going to two REBIRTH units – those on Large Animal Models for Myocardial Repair and on Tissue Engineered Heart Valves – for three years. The project's aim is to promote Moldova's 'Smart Specialization Strategy' by expanding the field of nanomaterials for biomedical applications. The idea is that, in this way, collaboration with strategic partners of leading European centres will enhance scientific excellence at the National Centre for Materials Study and Testing (NCMST), part of the Technical University of Moldova. The two leaders of the abovementioned REBIRTH units and members of the Cardiothoracic, Transplantation and Vascular Surgery team at MHH, Serghei Cebotari and Andres Hilfiker, have a role in this project. It is to provide initial and in-service training to a new generation of highly qualified researchers, thus enabling them to further develop the fields of nanomaterials and biomedicine in Moldova.

Centre now represented in expert working groups for NIH project

Professor Nils Hoppe, who heads the REBIRTH unit on Ethical and Legal Dimensions, is now analysing differences and commonalities in the regulation of genome research. He is doing so in conjunction with 31 ethical and legal experts from all over the world in a National Institutes of Health (NIH) project called 'Regulation of International Direct-to-Participant Genomic Research'. In this project, coordinated by Louisville University (USA) and McGill University (Canada), the 32 experts are seeking to jointly draw up examples of best practice and develop policy options for the ethically justifiable and legally enforceable regulation of research in which subjects and patients directly participate.

Increasingly, new technologies are emerging such as genetic tests that are available online (direct-to-consumer testing), which allow genomic studies to be conducted with the direct participation and patients and subjects. Such testing, which does not require medical personnel in doctors' practices or hospitals, is becoming more and more common. Use of these technologies inevitably entails transnational and global exchange involving consents, data and materials. This gives rise to substantive ethical and legal issues that this project aims to resolve. Professor Hoppe of the 'Centre for Ethics and Law in the Life Sciences' (CELLS) will provide the project with input pertaining to the German legal system.

CELLS has, in the past, already contributed to preparatory work. Moreover, CELLS spin-off consentris GmbH is working on technical aspects of dynamic consent models in biomedical research and can put to good effect the expertise available there.

Hübner und White awarded

Professor Dietmar Hübner (REBIRTH unit 10.7 on Ethical and Legal Dimensions) and Lucie White, Ph.D. (Institute of Philosophy, LUH), have been awarded the 'DGPPN-Preis für Philosophie und Ethik in Psychiatrie und Psychotherapie 2017'. This accolade, presented by the German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN), is for their work on the issue of whether neurosurgical interventions such as deep brain stimulation (DBS) can be justified in persons classified as 'psychopaths'. In their research, Hübner and White demonstrate that such procedures cannot meet basic bioethical standards, particularly the norms of individual medical benefit and of voluntary informed consent, even if these interventions are understood as curing what is objectively a disease, and even if the psychopath gives consent to this type of procedure. This constellation casts doubt on whether the proposed measures could be ethically justified in either research or therapy.

Publication

Hübner D, White L, "Neurosurgery for Psychopaths? An Ethical Analysis", American Journal of Bioethics – Neuroscience (AJOB Neuroscience) *7, 3 (2016), 140–149.*

A social walk with scientific value

"Everything's easier, and exercise has now become part of my routine," says Christa Schäfer. She is from Extertal, a municipality serving as the location for REBIRTH's 'active 60+' trial. On the evening of 10 July, together with over 50 other participants of the study, she hiked the *Sternberger Rundweg* circular trail. This group walk took place at the invitation of Professor Axel Haverich, director of the Department of Cardiothoracic, Transplantation and Vascular Surgery (HTTG) at Hannover Medical School (MHH), whose brainchild the study is, and Professor Uwe Tegtbur, director of MHH's Institute of Sports Medicine.

Afterwards, the hiking party fetched up in the beer garden of the local *Burg Sternberg* hotel. "I'm delighted we were able to mobilize so many people for the study and for this walk," says Professor Haverich, who himself hails from this neck of the woods. He was visibly impressed by the sense of commitment and camaraderie that emerged among both the participants and local GPs during the trial. Professor Tegtbur adds: "The subjects have done extremely well in terms of exercise performance and the degree of activity." Such consistent participation is rare in studies like this. "Over the past few months, I've often seen participants from all parts of our municipality combining exercise with their everyday routine by doing fitness walking and the like," comments Monika Rehmert, mayor of Extertal. She knows who these people are from their regular appearance at the town hall over the past six months for various strength measurements and other meetings. Among the supporters is Dr Axel Lehmann, CEO of the district authority. "We can use the scientific studies as a basis for developing long-term measures to improve the health of Lippe district's inhabitants. So these exercise schemes are important elements in enhancing the provision of healthcare and education here," Dr Lehmann stresses.

Because participation has been so enthusiastic, the study team is now extending the trial by a further six months. Professor Haverich explains why: "Increasing the study's duration will, among other benefits, enable us to obtain more reliable data on different parameters, and a longer training phase will mean a more long-lasting positive impact for the subjects."

The 'REBIRTH active 60+' study

The aim of this study is to enhance the body's ability to cope with stress, and regenerative capacity, through daily activity and exercise – and thus improve the quality of life. A total of 90 people aged 60 and above from the Lippe district have been taking part in the 'REBIRTH active 60+' trial since November 2017. Under this study, organized by MHH in conjunction with several local GP surgeries in Extertal, they have been doing regular physical training since January 2018.

A summer holiday in the lab

From 30 July to 3 August 2018 – designated 'Research Week' (*Forscherwoche*) – 12 school pupils from the Hannover region defied the summer heat to meet up at a lab especially designed for them. At the *Erich Kästner* secondary school in Laatzen they experimentally explored various issues surrounding diabetes. The 16- to 20-year-olds began by finding out which experiments were most conducive to answering these questions, and then carried them out as independently as possible. They were assisted by three supervisors, including Theresa Huntemann, who is doing a Research Gap Year in the REBIRTH unit on miRNA in Myocardial Regeneration, and Hendrika van Waveren from the School Biology Centre's Life Science Lab. Ms van Waveren organized what was already the seventh Research Week: "Our aim is to awaken enthusiasm among the youngsters for research work and provide guidance with careers choices."

At the end of the week, the pupils presented their findings to a 'panel' of experts in the form of posters. They explained how they made insulin in a Petri dish, how they were able to use bacteria to produce insulin on a large scale, and how they applied the Elisa test to identify candidates for organ transplantation (i.e. those with the mildest rejection reaction). Among the specialists present this year were Professor Tobias Cantz (REBIRTH unit on Translational Hepatology and Stem Cell Biology), Anna Rafiei Hashtchin and Maximilian Schinke (both of the REBIRTH unit on Translational Haematology and Congenital Disease), and Lika Drakhlis (REBIRTH unit on Mass Production of Pluripotent Stem Cells and Derivates). Drakhlis is part of the 'first generation' that van Waveren had motivated to pursue a science subject 10 years previously. Which was why she was among the four experts who rounded off the Forscherwoche with an account of their day-to-day research work and their careers to date. Professor Cantz gave a report, too – on how he became a liver researcher.

Young Investigator Award for Annika Heß

At the Society of Nuclear Medicine and Molecular Imaging Annual Meeting at Philadelphia, USA in June, Ph.D. student Annika Heß (member of the 2016 class of the Ph.D. programme in Regenerative Sciences, REBIRTH unit on Radionuclide Molecular Imaging) received the Cardiovascular Council's Young Investigator Award. Her abstract, entitled 'CXCR4-targeted imaging of leukocyte mobilization after myocardial infarction', demonstrated the prognostic value of the inflammatory signal identified by positron emission tomography in the first days after myocardial infarction in mice for acute left ventricle rupture and long term ventricular function. Pharmacologic blockade of CXCR4 early after myocardial infarction prevented rupture and improved contractile function at 6 weeks post-infarct. This work emphasizes the value of targeted and timed therapy to achieve balance in the inflammatory cascade after cardiac ischemia to improve outcome.

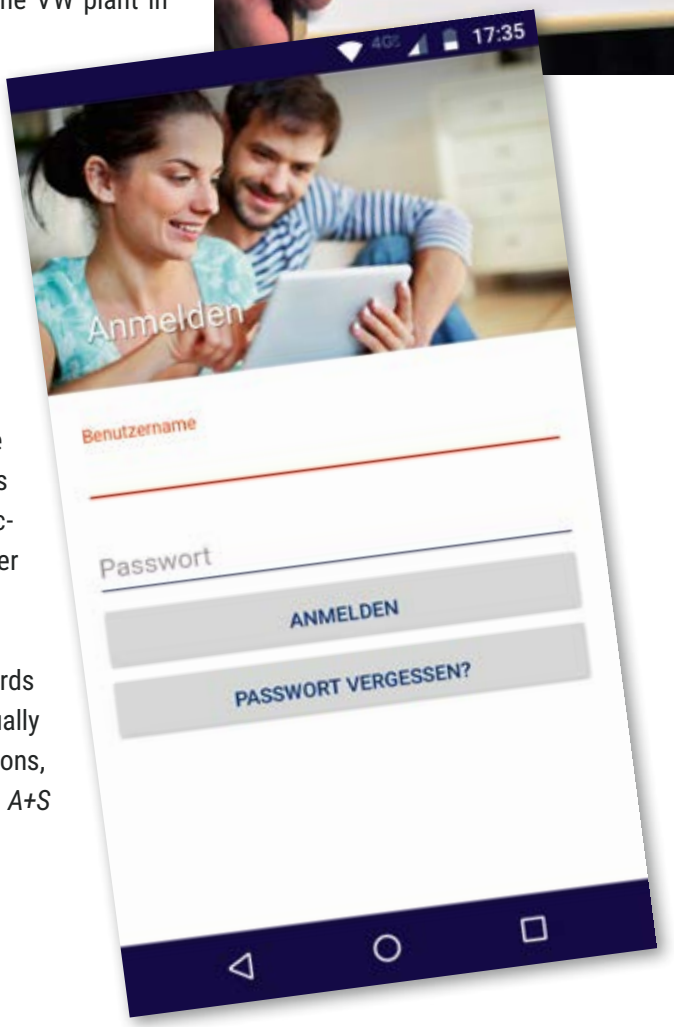
Publication

Heß A, Wittneben A, Kropf S, Wester HJ, Bengel FM, Thackeray JT. CXCR4-targeted imaging of leukocyte mobilization of myocardial infarction. J Nucl Med. 2018;59(Suppl):37.

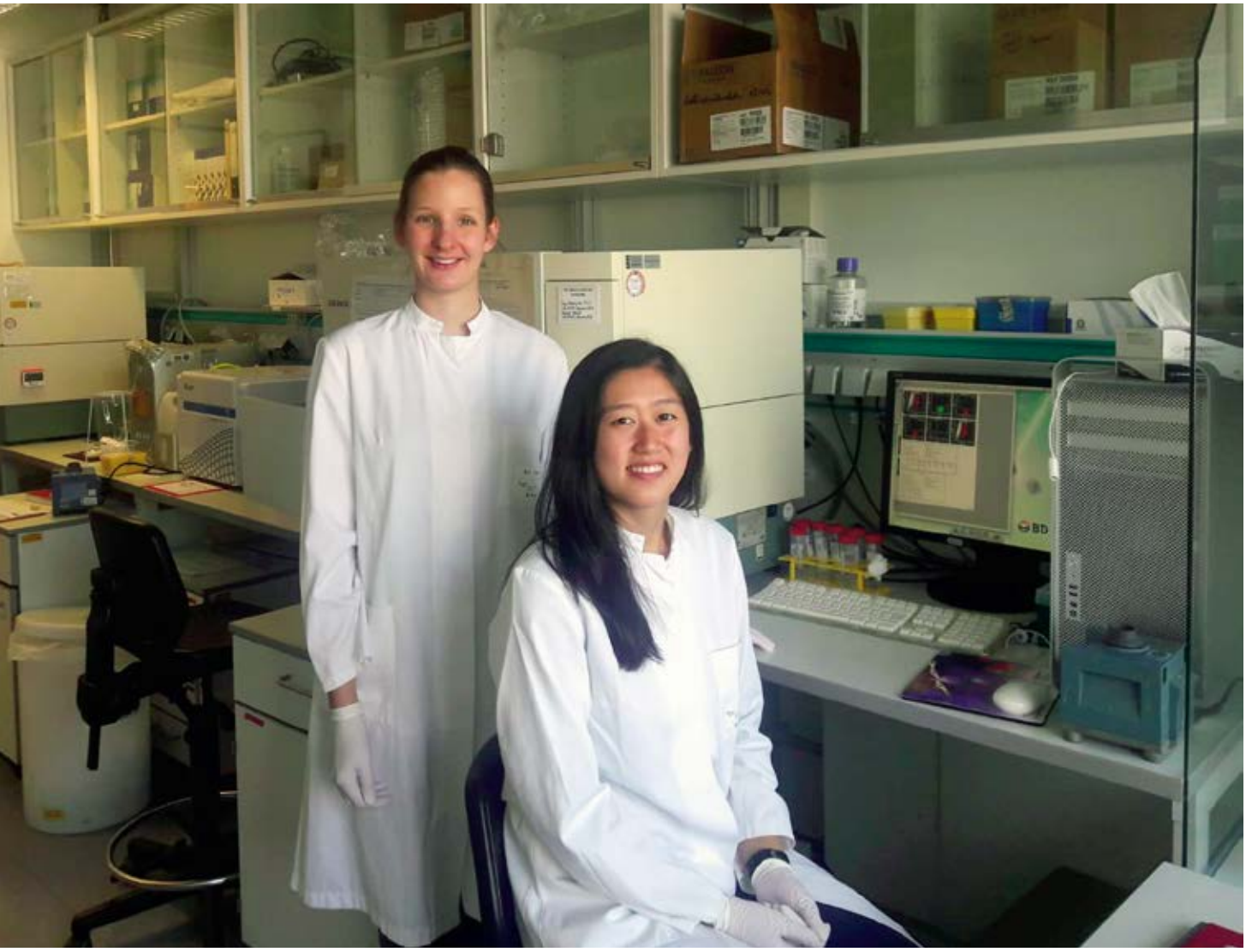
‘REBIRTH active’ app wins award

A ‘REBIRTH active’ app has won one of five dfg Awards – leading accolades in Germany’s healthcare system – under the category ‘Digital transformation in the healthcare sector: focus on statutory health insurers’. The prize, for conceiving and executing a digital app and a wearable solution for preventing and treating metabolic syndrome in the context of workplace health promotion, was presented in Hamburg on 7 June 2018.

Hannover Medical School (MHH) collaborated with four organizations – AUDI BKK, Volkswagen (VW) AG, Five Topics AG and d.evelop AG – in creating the app for use in the workplace health promotion scheme at the VW plant in Wolfsburg. Under this scheme, called ‘Get Moving!’, almost 300 employees at the factory are currently following personalized physical-training plans aimed at enhancing their health. The app serves as an information and communication medium: staff at MHH’s Institute of Sports Medicine can upload information that participants can view, such as recipe ideas, running tips, appointment reminders and news about the rest of the study. (This health promotion strategy is based on the outcomes of the ‘REBIRTH active’ trials conducted by the REBIRTH Cluster of Excellence.)



This year was the 10th time these dfg Awards have been presented. They are given annually by publisher MC.B and two of its publications, *dfg – Dienst für Gesellschaftspolitik* and *A+S aktuell – Ambulant und Stationär aktuell*.



from left: Denise Klatt und Erica Cheng.

From Canada to Hannover

Twenty-one-year-old Erica Cheng – a Biology undergraduate at the University of British Columbia in Vancouver, Canada – visited Hannover under the DAAD's RISE Germany programme (see box). From 4 June to 21 August 2018, she spent her research internship at the Institute of Experimental Haematology (IEH), supervised by Denise Klatt, a doctoral student in the Regenerative Sciences Ph.D. programme. During her internship, Ms Cheng used the gene-editing tool CRISPR-Cas9 to treat a hereditary immune disorder, chronic granulomatous disease, in an iPSC-based model. She also had the opportunity to learn skills such as harvesting bone marrow, virus production and granulocyte differentiation. In addition to gaining research experience, the Canadian student enjoyed being

able to pursue her interests in German culture and history. In particular, she loved the ability to travel at weekends to cities such as Hamburg, Berlin and Munich. "I'm thankful to have met so many wonderful people in the lab, and wish them all the best in the future," Ms Cheng says. And her time at the IEH has given her a career goal: to study haematopoietic diseases.

Denise Klatt's experience of the programme has also been positive: "The DAAD RISE Germany internship offers a great opportunity to share your knowledge with students and to get a first taste of teaching. And what you get in return is active support with your Ph.D. project."

Financial assistance for the scholarship-funded place at the Institute of Experimental Haematology was provided by DAAD and the REBIRTH Cluster of Excellence.

Deadlines - RISE Germany

Submission of internship offers:
1 September – 15 October 2018

Ranking of applicants:
21 January – 3 February 2019

The RISE Germany programme: Research Internships in Science and Engineering

The RISE Germany programme, supported by the German Academic Exchange Service (DAAD), offers summer research internships in science and engineering to undergraduate students from Canada, the USA, the UK and Ireland. Internships last between 10 and 12 weeks and take place in higher-education centres and non-university research institutions throughout Germany. Doctoral students in the life sciences / natural and engineering sciences have the opportunity to include their offer of an internship on a DAAD database so that RISE students can apply. The doctoral students act as supervisors and personal mentors to the interns. With this support, students have the opportunity to gain valuable research experience and explore German culture.

Overall, the DAAD's RISE Germany programme strives to promote international student exchange in the fields of science and engineering. By providing an opportunity to experience Germany first-hand, the programme hopes to inspire undergraduate students to return to Germany for future research and study opportunities.

https://www.daad.de/rise/de/rise-germany/

A successful HBRS team (from left): Jenny Lam and Anna-Lena Neehus in the lab.

Joining forces for success

Interdisciplinary team develops human platform for MSMD

Hannover Medical School (MHH) has a graduate school for students of various disciplines. Called 'Hannover Biomedical Research School' (HBRS), it provides opportunities such as a Master's degree in Biomedicine and a 'Structured Doctoral Education' (StrucMed) programme for medical students, the aim being to get the next generation of scientists and physicians excited about research work. "Joint student projects involving both of these broad disciplines are an excellent way of promoting synergy between basic scientific research and medical translation from an early stage," says Dr Nico Lachmann, who heads the REBIRTH unit on Translational Haematology of Congenital Disease at MHH's Institute of Experimental Haematology.

His interdisciplinary team investigates a rare blood condition called 'Mendelian susceptibility to mycobacterial disease' (MSMD). This is a complex immune disorder that may be triggered by various mutations resulting in the body's scavenger cells (macrophages) no longer being able to ward off invading pathogens. If the young patients are affected by the most dangerous mutation variant of MSMD (IFNgR deficiency), they rarely live to reach adolescence. "The limited treatment options for MSMD prompted me to find out more about this condition. Here on the MHH campus, we have excellent scientists, medics and students in a wide range of disciplines. Why not build on this and explore new ways of interacting?" says Lam, who is – under the StrucMed programme – doing her doctoral thesis within REBIRTH unit Translational Hematology of Congenital Disease. Together with Anna-Lena Neehus, a Master's student in Biomedicine, she contributed to a platform dedicated to researching new approaches to treating MSMD. "We cooperated closely with physicians to obtain samples from different patients. By reprogramming these cells into induced pluripotent stem cells or iPSCs, we can now provide scientists and doctors all over the world with a cell of unlimited availability that can be transformed into the target cell, the macrophage," explains Neehus. The team will follow up on this approach so that the very next interdisciplinary generation of students can devise a treatment for MSMD based on these findings.

Getting active in Warsaw

The atmosphere was relaxed – just right for trying things out and joining in. This was an open-air event with a difference: the 22nd Science Picnic (SCP) held at the National Stadium in Warsaw on 9 June 2018. The theme was 'Movement', and some 250 exhibitors shared science and technology-related experiments and insights with the visitors in a clear and comprehensible way. "The event was especially popular with young families with children; they showed great interest in the various stands and were keen to try out the wide range of things on offer," reported Pauline Bayerle who, in conjunction with Hedwig Theda Stenner and Christin Bormann, had gone to Warsaw to present the 'REBIRTH active' trials and to get the visitors moving. To help with communication, the three sports scientists from Hannover Medical School's (MHH) Institute of Sports Medicine were actively supported by a team led by Matthias Rehm, academic relations officer at the German Embassy in Warsaw. They translated the main points arising from the REBIRTH studies and, in Polish, encouraged the initially cautious visitors to have a go and get active. "The exercise sessions themselves also worked well on a non-verbal level, with the sports scientists showing a lot of physical commitment and injecting a lot of fun," says Pauline Bayerle.

The MHH team had 15 Garmin watches for visitors to try out, enabling them to take their wrist pulse. The sports scientists did simple exercises with the visitors, such as star jumps and jogging on the spot, and monitored heart frequency as it increased and then normalized after the activity. What went down particularly well with the children was a dice, each side of which indicated an activity in the categories of stamina, strength, agility and coordination. All of the youngsters got to throw the dice once and then try out the exercise with the sports scientists.

Contact between the German Embassy – which has, together with German partners, been involved in this science show since 2003 – and the REBIRTH Cluster of Excellence was arranged by Germany's Federal Centre for Health Education (BzGA).

The SCP is organized by the Copernicus Science Centre in Warsaw, the Polish Academy of Sciences (PAN), Polish Radio and the National Stadium in Warsaw.

What are you working on and why?

Our group previously identified a novel secreted protein, myeloid-derived growth factor (MYDGF), in acute myocardial infarction patients. MYDGF was found to have potent cardioprotection effects. My Ph.D. project is to identify its cell surface receptors, then to investigate their roles in MYDGF-mediated beneficial actions. This work is going to enable a more comprehensive assessment of MYDGF as a modulator and a potential treatment for myocardial infarction.

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

Initially, I was involved in a Dr. med programme at MHH. I learnt about REBIRTH by attending a seminar. It was about molecular biology of heart failure. The instructor provided such a fascinating lecture, not only presenting highly relevant research benchmarks but also tutoring attendees to make physiological measurements of the murine heart. Later, I obtained more information about REBIRTH's well-designed training system and high-quality academic platform from another REBIRTH student in our lab. These things impressed me a lot, so I decided to apply for this Ph.D. programme.

What do you like about Hannover Medical School?

There are several aspects of Hannover Medical School I like in particular. Firstly, it has plenty of education and research resources. Here I can always find attractive knowledge-based or method-based seminars to attend. Moreover, the campus is quiet and very suitable for doing research. Lastly, it is international and diverse. In our lab, for instance, there are people from South Korea, Iran, Romania, China and of course Germany. I am enjoying studying and working in such a friendly and inclusive environment.

In your opinion what (crazy / realistic) innovation will have come out on top in 2030?

Sophisticated artificial intelligence in disease diagnosis and treatment empowers people to manage their own health at home.

Ph.D. Programme *Regenerative Sciences*

Who is Who

***Xuekun Wu** (27) from China started his Ph.D. in 2017, REBIRTH* Unit Secreted factors and non-cell-based strategies for cardiac regeneration