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Funding: The Heisenberg Programme

Funding Research Programmes at German Universities for Researchers Who Qualify for a Professorship

Five cardiovascular scientists have been funded by the Heisenberg Programme over the past 4 years. They describe the funding and their research to Jennifer Taylor, BSc, MSc, MPhil.

The Heisenberg Programme of the German Research Foundation (Deutsche Forschungsgemeinschaft [DFG]) is aimed at young researchers in all disciplines who qualify for a professorship. It includes German researchers returning to Germany and foreign researchers who would like to pursue an academic or a scientific career in Germany. Heisenberg professorships and fellowships allow scientists to pursue their field of research, but an application may also be made for additional funding from the DFG in the form of a research grant to work on specific projects. Projects must be carried out at a German research institute. Research grants are for 3 years, but can be renewed.

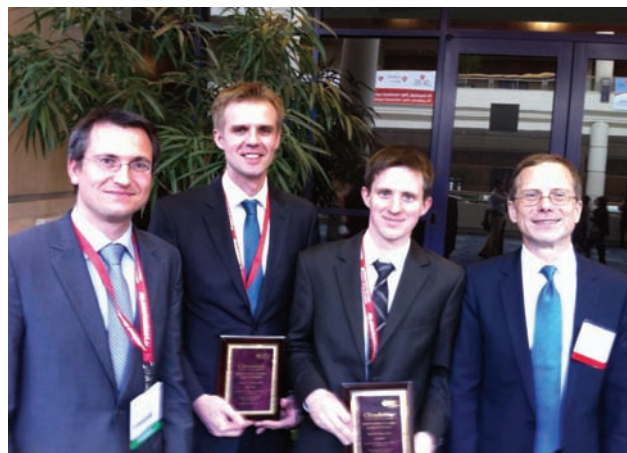
Heisenberg professorships provide funding for a temporary professorship at a German university, which must be continued from the university's own budget after the funding period expires. They are intended to enable scientists to establish themselves as a professor at a German university and to enhance the university's visibility. Successful applications depend on the scientist's academic qualifications and the university's case for how the professorship will raise the institution's profile and contribute to its structural development. Final decisions on a Heisenberg professorship are made on the basis of a scientific review led by the DFG and the university's completion of the professorial appointment process. Funding is normally for 5 years. An interim evaluation is conducted by the DFG after 3 years; if successful, it leads to a further 2 years of funding by the DFG, followed by a transfer of the professorship to the university's budget.

Heisenberg fellowships provide a grant of €4450 per month for living expenses plus a monthly allowance of €103 for direct project costs (books, consumables, etc) and travel expenses (eg, conference attendance). A childcare allowance is available for children up to the age of 12. Researchers can apply for travel and foreign allowances for a research stay abroad or to attend conferences. Requests for publication expenses are also considered. Fellowships enable researchers to dedicate their time to research and

can be converted into a Heisenberg professorship during the funding period if certain requirements are met. Over the past 4 years, 5 cardiovascular scientists have been funded by the Heisenberg Programme.

1. Lars S. Maier, MD, FAHA, FESC, Heisenberg professor, Department of Cardiology and Pneumology, Heart Centre Göttingen, Göttingen, Germany

Professor Maier has held a Heisenberg professorship for cardiovascular experimental electrophysiology and imaging at the Department of Cardiology and Pneumology (chaired by Gerd Hasenfuss, MD; see <http://circ.ahajournals.org/content/119/9/f49>), Heart Centre Göttingen, since 2009. He is also a senior physician specialising in cardiology and internal, intensive care, and emergency medicine.



Professor Hasenfuss (right) and Professor Maier (left) were the last authors of an article on differential cardiac remodeling in preload versus afterload which was awarded *Circulation's* Best Basic Science Paper 2010. First shared author Karl Toischer, MD, is 2nd from right, and second shared author, Adam Rokita, is 2nd from left. Photograph courtesy of Professor Maier.



Members of the lab group working with Professor Maier at the annual run during the German Heart Meeting 2010 in Mannheim, Germany. From left to right: Anika Mallwitz (who died in 2011), Kay Neuma, Nico Hartmann, Azadeh Azizian, Professor Maier, Malte Tiburcy, MD, and Stefan Wagner, MD. Photograph courtesy of Professor Maier.

Professor Maier graduated from the University of Göttingen, received his MD from the University of Freiburg, Freiburg, Germany, and joined the Department of Cardiology and Pneumology at the University of Göttingen in 1999. After a 2-year postdoctoral period in the lab of Donald M. Bers, PhD, in Chicago, IL, he returned to Göttingen in 2003 funded by a DFG Emmy Noether Fellowship.

As a clinician scientist, Professor Maier's main area of interest is excitation-contraction coupling in the heart. His group discovered that Ca^{2+} /calmodulin-dependent kinase II (CaMKII) phosphorylates cardiac sodium channels leading to a persistent or late sodium current.^{1,2} Both late sodium current³ and CaMKII-dependent sarcoplasmic reticulum calcium leak⁴ were shown to be involved in atrial fibrillation. CaMKII was also found to be involved in cardiac hypertrophy in myocardial samples from patients with increased afterload due to aortic stenosis but not during increased preload.⁵ His group also showed that CaMKII inhibition improves myocardial contractility in isolated muscle preparations from patients with end-stage heart failure.⁶ Professor Maier says, "Recently our group has focused on translational aspects and investigated late sodium current inhibition in diastolic heart failure in vivo."⁷

Professor Maier is a member of numerous national and international medical and biophysical societies and has co-authored ≈ 100 articles with a cumulative impact factor of 550 and 3300 citations. He has also been involved in important international collaborations, including EUGeneHeart (Genomics of Myocyte Signalling to Treat and Prevent Heart Failure), CONTICA (Control of Intracellular Calcium and Arrhythmias), and the Fondation Leducq Transatlantic Networks of Excellence Programmes "Alliance for CaMKII Signalling in Heart Disease" and "Redox and Nitrosative Regulation of Cardiac Remodelling."

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2. Alma Zernecke, MD, junior research group leader, Rudolf-Virchow Centre/DFG Research Centre for Experimental Biomedicine, University of Würzburg, Würzburg, Germany

Dr Zernecke was awarded a Heisenberg fellowship in April 2009. Her research group is in part supported by a Junior Research Group grant provided by the Rudolf-Virchow Centre of the University of Würzburg, which is a DFG-funded research centre.

Dr Zernecke's research aims to understand the immune pathogenesis of atherosclerosis. By targeting specific cytokines and their receptors in atherosclerosis-prone mouse models, the group addresses the functions of different immune cell subpopulations in atherosclerosis. A particular focus lies on cell interactions at sites of inflammation and also within lymphatic tissue, and the role of these cells in shaping specialised immune responses. The group recently demonstrated that dendritic cells expressing the chemokine ligand 17 are present in advanced atherosclerotic lesions, and that chemokine ligand 17 acts as a central regulator of regulatory T cell homeostasis.¹

Dr Zernecke also focuses on microRNAs and the identification of the expression and function of individual microRNAs in the regulation of immune responses in atherosclerosis. She explains, "We hope that our work will contribute to a better understanding of the complex equilibrium and interplay of immune cell subpopulations that contribute to the process of atherosclerosis and help guide the way towards the identification of novel markers and targets for therapeutic approaches for treating this disease."

Dr Zernecke previously worked on chemokines and their receptors that are important in the accumulation of

leukocytes at sites of inflammation in the lab of Christian Weber, MD (see <http://circ.ahajournals.org/content/119/24/f139>) when he was director of the Institute of Molecular Cardiovascular Research, RWTH Aachen, Aachen, Germany. She says, “I had, in addition, become interested in chemokine functions beyond their role as chemoattractants and, in particular, their functions in controlling the survival and cell homeostasis of leukocyte populations.”

In collaboration with Steffen Jung, PhD, of the Weizman Institute, Tel Aviv, Israel, for instance, they observed that the absence of CX3C chemokine receptor 1 resulted in a significant reduction in monocyte survival and blood monocyte counts. They also identified CX3C chemokine receptor 1 as an important survival signal for these cells and a mechanism for how this chemokine/receptor axis promotes atherosclerosis development by preventing the death of monocytes and foam cells.²

Another study investigated the role of chemokine (C-X-C motif) ligand 12 and its receptors, C-X-C chemokine receptors type 4, in atherosclerosis. They observed that disruption of this chemokine/receptor axis aggravated diet-induced atherosclerosis in mice, which was associated with a deranged neutrophil homeostasis. An increased content of this cell population within plaques, together with an enhanced plaque growth furthermore revealed an important contribution of neutrophils to atherosclerosis.³ Further research revealed that delivery of microRNA-126 by apoptotic bodies induces expression of chemokine (C-X-C motif) ligand 12 and limits atherosclerosis.⁴

“Beyond chemokines, little is still known about the role of many other and related cytokines and microRNAs in regulating the function and plasticity of immune cells in the pathogenesis of atherosclerosis,” says Dr Zerneck. “I have now embarked on these studies in my own independent research group.”



Dr Zerneck (5th left) and her research group at the University of Würzburg. Photograph courtesy of Dr Zerneck.

3. Tienush Rassaf, MD, FESC, professor of internal medicine/cardiology and attending physician, Department of Cardiology, Pulmonary Diseases and Vascular Medicine, University Hospital Düsseldorf, Düsseldorf, Germany

Professor Rassaf is an attending physician certified in internal medicine, cardiology, angiology, and emergency medicine in the Department of Cardiology, Pulmonary Diseases and Vascular Medicine chaired by Malte Kelm, MD. He received a Heisenberg fellowship in 2009 and has held a Heisenberg professorship since 2010. His research programme focuses on clinical strategies that minimise myocardial ischaemia–reperfusion injury, and he is using a 3-step approach to characterise signalling pathways and evaluate potential therapeutic interventions. The first part aims to determine the mechanisms that activate endogenous and pharmacological nitrite to nitric oxide independent of oxygen levels in the myocardium. Evidence based on animal models suggests a relevant tissue protection by nitrite. Determination of the pathways and circumstances for nitrite activation may build the basis for future translational approaches using nitrite therapeutically to reduce ischaemia–reperfusion injury.

Second, accumulating evidence indicates that the immune system is highly relevant in reperfused myocardium. Specific mediators of the ischaemia–reperfusion-associated immune response may provide new targets for clinical treatments. Macrophage migration inhibitory factor has been shown to play a key role during acute ischaemic events, but the exact mechanisms by which it protects the heart are unknown. Structural analyses indicate that it might undergo posttranslational modification. This part of the programme aims to investigate the reactions between nitrite/nitric oxide and macrophage migration inhibitory factor as part of the protective signalling during ischaemia–reperfusion injury and as a potential therapeutic target.

The third part of the research programme relates to new imaging techniques with a particular focus on fusion imaging

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Professor Rassaf (centre, 7th left) and his group at University Hospital Düsseldorf. He says, "My group consists of 1 postdoc, 1 technician, 4 physician scientists, 2 graduate students, and 4 medical students." Photograph courtesy of Professor Rassaf.

(magnetic resonance, angiography, computed tomography, ultrasound) to determine the different modalities of myocardial ischaemia–reperfusion injury in patients.

In the past, Professor Rassaf has researched the physiological and pathological roles of nitrogen oxides in cardiovascular function. First, he considered the endocrine effects of nitric oxide produced enzymatically via nitric oxide synthases. It was controversially discussed whether nitric oxide could exert its effects at remote sites to the place of origin. By developing new high-performance liquid chromatography and chemiluminescence-based techniques, Professor Rassaf and his colleagues demonstrated that nitric oxide can be transported as nitroso species in the blood in humans, thus significantly extending the half-life of nitric oxide.^{1,2}

Professor Rassaf also investigated nitric oxide synthase-independent nitric oxide generation. His and other groups have demonstrated that nitrite in the blood and in tissues where levels are particularly high represents a pool for bioactive nitric oxide along the physiological oxygen gradient.^{3,4} Nitrite was evaluated as a potential pathway for oxygen-dependent signalling in the myocardium, with partially understood implications for physiology and pathology.

The final area was nitrite as a regulator for signalling in hypoxia. In a murine ischaemia–reperfusion model, Professor Rassaf showed that the application of nitrite reduced myocardial ischaemia–reperfusion injury, optimised left ventricular function, and reduced the formation of reactive oxygen species by modulating mitochondrial respiration.⁵ Ablation of myoglobin in myoglobin-deficient mice abrogated these protective effects. He says, "Interestingly, the first translational studies in humans corroborate the experimental findings."

"Taken together, these studies provide the basis for the Heisenberg professorship," says Professor Rassaf. "This research programme will evaluate specific underlying mechanisms and translational approaches towards a potential treatment for patients." The professorship enables him to work full time as a cardiologist in the clinic and run a high-level experimental science programme."

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4. Torsten Doenst, MD, FACC, FAHA, chair of the Department of Cardiothoracic Surgery, University Hospital Jena, Friedrich Schiller University of Jena, Jena, Germany

Professor Doenst received a Heisenberg professorship in 2007. It provided €400,000 for 5 years but ended in 2010 when he accepted his current position in Jena. During the professorship, he was full professor in cardiac surgery at the University of Leipzig, Leipzig, Germany, and during the last 8 months, he was also the leading staff cardiac surgeon at the Heart Centre Leipzig, University of Leipzig. Professor Doenst's research focuses on cardiac metabolism.

Before receiving the Heisenberg professorship, Professor Doenst investigated the relationship between energy substrate metabolism and the contractile function of the heart. He and his colleagues looked at mitochondrial function under pressure overload. "We identified a specific complex-related defect in the respiratory chain associated with pressure overload-induced mitochondrial and contractile dysfunction,"¹ he says. "We therefore suggested that a metabolic defect may be the cause of contractile dysfunction and heart failure." Professor Doenst has also found that long-term changes in workload differentially affect the maximal respiratory capacity and ischaemia tolerance of isolated mitochondria from unloaded and overloaded hearts.²

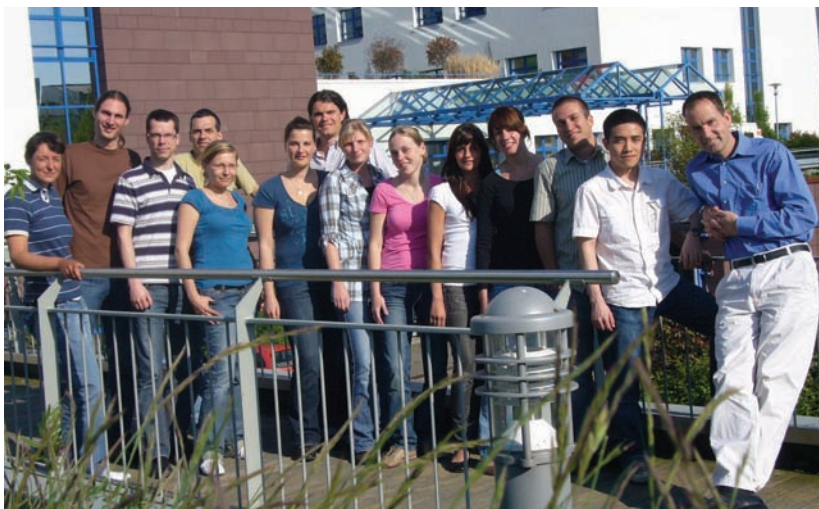
This research experience helped Professor Doenst secure the Heisenberg professorship. His success was also influenced by the fact that he had established his own independent metabolic research activity as a resident in cardiac surgical training in Freiburg and, later, as a staff surgeon in Freiburg and Leipzig. He was also part of the Emmy Noether programme of the DFG, which awarded €660,000 between 2000 and 2003 for the project "Mechanisms of Postischaemic Insulin Action." This project revealed that insulin improves postischaemic contractile function

through a mechanism similar to ischaemic preconditioning.³ Insulin's effect on recovery may be dependent on ischaemia-induced protein kinase C activation.⁴

During the Heisenberg professorship, Professor Doenst investigated the topic "Dysregulation of Energy Substrate Metabolism as a Cause for Heart Failure." He says, "Thus far, I have been the only cardiac surgeon in the Heisenberg programme, and there are only a few surgeons from other disciplines."

Professor Doenst's interest in cardiac metabolism led to a review article in 2008, in which he outlined why cardiac surgeons should be interested in cardiac metabolism and how a greater understanding of energy metabolism could improve surgical outcomes.⁵ A subsequent review in 2011 focussed on metabolic remodelling in heart failure.⁶

In his earlier research on cardiac metabolism, Professor Doenst published an article in *Circulation* in 1998 showing the limitations of using [18F]2-deoxy-2-fluoroglucose to quantify myocardial glucose uptake in human heart.⁷ Specifically, [18F]2-deoxy-2-fluoroglucose underestimates glucose uptake during reperfusion in the presence of fatty acids, but in the fasted state it overestimates glucose uptake during ischaemia. Professor Doenst also co-authored an article in *Nature Medicine* when he was a fellow with Heinrich Taegtmeyer, MD, DPhil, at the University of Texas, Houston, TX, in 1998, revealing that the reactivation of fetal genes may underlie the functional improvement of an unloaded failing heart.⁸ In 1999, he wrote an article in *Circulation Research* showing that the stimulating effects of the α and β adrenergic pathways on glucose uptake are independent of changes in cardiac performance.⁹



Professor Doenst (1st right) and his group at the University of Leipzig in 2009. Photograph courtesy of Professor Doenst.

5. Sonja Schrepfer, MD, PhD, Heisenberg professor, University Heart Centre Hamburg, Hamburg, Germany, director of the Transplant and Stem Cell Immunobiology Lab, Hamburg, and consulting professor, Stanford University, Stanford, CA

Professor Schrepfer received a Heisenberg professorship for transplant immunology and stem cell immunobiology in cardiac surgery in 2009. It provided a W3 professorship, personnel, consumables and materials, and article costs for 5 years to investigate the immunobiology of pluripotent human stem cells. Despite advances in surgical procedures, mechanical assistance devices, drug therapy, and organ transplantation, >50% of patients with congestive heart failure die within 5 years of initial diagnosis. Stem cell transplantation holds promise for treating ischaemic heart disease, but several hurdles that preclude clinical translation of such therapy need to be overcome, of which stem cell immunogenicity is a major concern.

Immunogenicity of human embryonic stem cells and their derivatives remains a controversial issue. In contrast to mouse embryonic stem cells, human embryonic stem cells express relevant levels of major histocompatibility complex class I antigens, which increase when the cells differentiate into cardiomyocytes. Professor Schrepfer and her group evaluate the antigenicity or immunogenicity of human embryonic stem cell-derived cardiac cells by investigating their immunological incompatibility and the adaptive immune response, especially in the inflammatory conditions of myocardial ischaemia.

In addition, Professor Schrepfer's group is attempting to suppress cellular and humoral rejection of transplanted human embryonic stem cells by genetically modifying them to overcome the immunological barrier. They have studied various delivery methods and gene therapy strategies. An alternative approach is to derive patient-specific induced pluripotent stem cells by transduction or transfection of pluripotency genes or proteins to reprogramme

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Professor Schrepfer (3rd right) and her colleagues at the Transplant and Stem Cell Immunobiology Lab, Hamburg. Photograph courtesy of Professor Schrepfer.

somatic cells into an “embryonic stem cell-like” state. “In theory, induced pluripotent stem cells would not face the same histocompatibility barriers as human embryonic stem cells because they are derived and transplanted into the same person,” says Professor Schrepfer. “However, it is questionable whether personalised induced pluripotent stem cell-based therapy will be economically feasible for the population at large. Furthermore, for acute diseases such as myocardial infarction, it would most likely be more effective if off-the-shelf products (eg, induced pluripotent stem cell-derived cardiac cells) can be administered in a timely fashion.”

Professor Schrepfer believes that it may be more feasible to create a universal induced pluripotent stem cell line, but an important hurdle facing their *in vivo* engraftment and function is the immunological barrier. Professor Schrepfer aims to decrease the immunogenic potential of human induced pluripotent stem cells by modulating their antigenic surface molecules using immunological and molecular biology techniques, such as *in vivo* bioluminescence imaging. Another goal is to achieve long-term survival by generating induced pluripotent stem cell-derived cardiac engineered scaffolds. This work is being done in collaboration with the pioneer of engineered heart tissue, Professor Thomas Eschenhagen, MD, in Hamburg, Germany. “The successful establishment of induced pluripotent stem cell engraftment and tolerance will eliminate the critical immunological barrier that presently precludes the successful application of cell-based regenerative therapy,” says Professor Schrepfer. “These are fundamental challenges that must be met before stem cell therapy can become a reality.”

Professor Schrepfer’s application for the Heisenberg professorship was strengthened by her preliminary work, which demonstrated a combination of experimental experience in stem cell research^{1–4} and transplant immunology.^{5–7} This research concentrated on the immunogenicity of solid organs and stem cells. They also developed techniques to

reduce the T cell-mediated response to donor cells and in that way induced a recipient tolerance against transplanted cells by genetically manipulating them.

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Jennifer Taylor is a freelance medical journalist.

Editor: Christoph Bode, MD, FESC, FACC, FAHA

Managing Editor: Lindy van den Berghe, BMedSci, BM, BS

We welcome comments. E-mail: lindy@circulationjournal.org

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