Funding: Kaltenbach PhD Scholarships

Supporting Medical Students and Graduates in Germany to Carry Out Clinical Cardiovascular Research

Recipients of a Kaltenbach scholarship in 2012 describe their research funded by the scholarship to Jennifer Taylor, BSc, MSc, MPhil.

Looking for MiRNA Patterns Specific for Patients at Risk of Developing Plaque Rupture

Judith Amann, medical student, Atherothrombosis and Vascular Biology Lab, Albert-Ludwigs-University of Freiburg, Freiburg, Germany, received a Kaltenbach scholarship for the project titled, “Detection of New MiRNAs as Biomarkers for Unstable Coronary Artery Disease Using Next-Generation Sequencing.” She says, “The scholarship provided me with the unique opportunity to do full-time research at the Baker IDI Heart and Diabetes Research Institute in Melbourne, Australia.” This exchange was possible due to collaboration between Professor Karlheinz Peter, MD, PhD, at Baker IDI, and Professor Christoph Bode, MD, PhD, chair, Department of Cardiology and Angiology, University of Freiburg.

Recent studies have shown that miRNAs, small RNAs that bind to mRNAs and so influence post-translational gene regulation, can serve as blood surrogate markers in different diseases. Professor Peter’s group has recently demonstrated that the vast majority of miRNA does not circulate freely in blood but is located in microparticles.

With next-generation sequencing, a method that can detect thousands of different known and potentially novel miRNAs, Ms Amann is analysing microparticle miRNA of patients who have stable and unstable coronary artery disease. She says, “I hope to find miRNA patterns that are specific for patients at risk of developing plaque rupture and thus could be used as a diagnostic test.”

Quantifying the Regurgitation Fraction and Left Ventricular Function in Chronic Aortic Regurgitation

Lenika Calavrezos, final year medical student, Functional Cardiovascular Magnetic Resonance in Congenital Heart Disease Research Group (head: Sohrab Fratz, MD, PhD, German Heart Center Munich, Technical University of Munich, Munich, Germany), received a scholarship to study aortic regurgitation. The Cardiovascular Magnetic Resonance Unit of the German Heart Center Munich is 1 of the few highly specialised centres for congenital cardiovascular magnetic resonance in the world and sees ≈600 patients with congenital heart disease each year.

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Professor Lopez-Sendon is last author of a recent article in Circulation that concludes that a lower cooling level may be associated with a better outcome in patients surviving out-of-hospital cardiac arrest secondary to a shockable rhythm. Page f148

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Optimal timing for aortic valve replacement in patients with chronic aortic regurgitation is not clear. Present guidelines recommend exercise stress testing to help in making the decision. However, techniques to directly quantify the regurgitation fraction during exercise have been described only sporadically and have applied disproportionately invasive methods. Cardiovascular magnetic resonance allows noninvasive and highly accurate quantification of the regurgitation fraction.

Ms Calavrezos says, “The aim of my study is to directly quantify the regurgitation fraction and left ventricular function in patients with chronic aortic regurgitation under submaximal physical exercise for the first time.” For this purpose, the research group developed a magnetic resonance imaging exercise device that causes little interference with image acquisition and is easy to use. Ms Calavrezos concludes, “The theory is that aortic regurgitation is reduced under physical exercise, which would question exercise as a decision criterion for intervention.”

Investigating the Role of Extracellular Microvesicles During Cardiovascular Development and Disease

Victoria Ekeh, BSc, MBBS, postgraduate fellow, Department of Cardiology, Heidelberg University Hospital, Heidelberg, Germany, obtained a BSc degree in zoology in Nigeria and then studied medicine at the University of Heidelberg. She obtained her licence to practice as a medical practitioner in 2012 and hopes to become a specialist in cardiology. She currently works in the Department of Cardiology at Heidelberg under David Hassel, MS, whose lab has a longstanding interest in the identification of novel molecular mechanisms involved in cardiovascular development and function.

Dr Ekeh’s project focuses on the role of extracellular microvesicles during cardiovascular development and disease. Dr Ekeh says, “Over the past decades, studies have shown that actively released microvesicles are involved in several tissue responses including angiogenesis. However, little is known about their role during cardiovascular disease and their potential as future therapeutic tools.”

Exploring the Underlying Pathomechanisms of Sodium Channelopathies

Thomas Fink, final year medical student, University of Heidelberg, has a strong interest in basic cardiovascular research and used his Kaltenbach scholarship to spend a focused period of time on his doctoral thesis. He is conducting his project in the Molecular and Translational Cardiac Electrophysiology Research Unit, Department of Cardiology, Heidelberg University Hospital, where his project supervisor is Patrick A. Schweizer, MD, and his thesis supervisor is Dierk Thomas, MD. The director of the department is Professor Hugo A. Katus, MD (see http://circ.ahajournals.org/content/122/7/f37).

The research team collaborates with the Max-Planck-Institute for Medical Research, Heidelberg (Michael Koenen, PhD), Department of Cardiology, University Hospital Muenster, Muenster, Germany, and the Centre for Cardiovascular Sciences, University of Birmingham, Birmingham, England (Larissa Fabritz, MD, and Professor Paulus Kirchhof, MD, see http://circ.ahajournals.org/content/123/24/f139). Mr Fink has been able to spend time in the collaborators’ labs, and his project focuses on the characterisation of a mouse model for human sodium channel-associated arrhythmia syndromes (sodium channelopathies). He says, “The management of patients with these disorders is often implantation of a defibrillator to prevent a fatal outcome, and causative therapies have not yet been established. We aim to explore underlying pathomechanisms to provide the scientific basis for the development of new therapeutic strategies.”

Investigating the Role of the Catalytic Phosphatidylinositide 3-Kinase Isoform p110alpha in Smooth Muscle Cells for Neointima Formation After Vascular Interventions

Joana Jesus, final year medical student, Professor Stephan Rosenkrantz’s [MD] Lab, University Hospital of Cologne, Cologne, Germany, received a Kaltenbach scholarship to investigate the role of the catalytic phosphatidylinositide 3 kinase isoform p110alpha in smooth muscle cells for neointima formation after vascular interventions.

Vascular restenosis after balloon angioplasty is a significant problem. Neointima formation is mainly caused by proliferation, migration, and survival of vascular smooth muscle cells. In this context, growth factors such as platelet-derived growth factor that activate receptor tyrosine
kinases play a significant role. Receptor tyrosine kinase-induced responses are largely mediated by activation of class IA phosphatidylinositol 3 kinase. The project aims to characterise the role of p110alpha for neointima formation using a genetic approach.

Previously, the group demonstrated that in vitro inhibition of the catalytic phosphatidylinositol 3-kinase isoform p110alpha completely abrogated growth factor mediated proliferation of vascular smooth muscle cells. Therefore, they generated smooth muscle-specific p110alpha-deficient mice to analyse in vivo the relevance of p110 alpha in restenosis formation after balloon angioplasty. The extent of neointima formation in carotid arteries was quantified in wild type, p110alpha-deficient, and heterozygous (p110alpha+/–) animals 4 weeks after angioplasty. In addition, they isolated aortic vascular smooth muscle cells and are currently analysing growth factor-mediated cellular proliferation, migration, and apoptosis.

**Developing a Noninvasive Diagnostic Imaging Technique for Inflammation and Necrosis After Ischaemia-Reperfusion Injury**

Alexander Maier, medical student, Department of Cardiology and Angiology I, University Heart Centre Freiburg, is using his Kaltenbach scholarship to conduct research in the Molecular Imaging and Proteomics Lab in Freiburg, where the principal investigator is Constantin von zur Mühlen, MD.

Mr Maier’s project involves molecular imaging of inflammation and myocardial necrosis in ischaemia-reperfusion injury in mice. The research group first established in vivo magnetic resonance imaging using a gadolinium-based contrast agent in mice with coronary artery ligation and ischaemia-reperfusion injury, which allowed detection of myocardial necrosis. Activated platelets in reperfused myocardium were then imaged using a contrast agent consisting of microparticles of iron oxide and a single-chain antibody targeting ligand-induced binding sites on activated glycoprotein IIb/IIIa. Both imaging strategies were then combined. Using these methods, activated platelets and myocardial necrosis were imaged in a simultaneous imaging strategy using magnetic resonance imaging.

**Expanding the Knowledge About the Genetic Background of Dilated Cardiomyopathy**

Akira-Sebastian Olbrich, medical student, Molecular Cardiology Lab, Department of Cardiology, Philipps University, Marburg, Germany, received a Kaltenbach scholarship to investigate polymorphisms in the cardiotrophin-1 gene and their relevance in the pathogenesis of dilated cardiomyopathy. He is supervised by Volker Ruppert, MD, and Professor Sabine Pankuweit, PhD.

The cardiotrophin-1 protein is a cytokine with hypertrophic and anti-apoptotic effects on cardiomyocytes. The research team’s hypothesis is that mutations in the cardiotrophin-1 gene cause altered gene and protein expression as well as altered protein localisation in the cell leading to aberrant growth characteristics of cardiomyocytes.

Based on single-strand conformation polymorphism analysis, 300 DNA samples from patients with dilated cardiomyopathy are being tested for sequence changes. In cases of confirmation of a mutation by DNA sequencing, descriptive studies by immunohistochemical staining of endomyocardial biopsies and analysis of gene expression of cardiotrophin-1 and selected target genes will be carried out.

**Examining the Consequences of Different Extracorporeal Circulation Systems**

Juliane Wolfram, resident in paediatrics, Greifswald University Hospital, Greifswald, Germany, used her Kaltenbach scholarship to study methods for cardiopulmonary bypass.

The study of 35 pigs compared a miniatuised cardiopulmonary bypass, a conventional open cardiopulmonary bypass, and an optimised method for cardiopulmonary bypass by analysing the pressure in the venous line at intervals of 250 ms, measurements with the bubble counter for bubble size and volume, and Doppler sonography to measure gaseous emboli in the left and right cerebral artery media.

Ms Wolfram says, “Despite the well-known advantages of the minimised cardiopulmonary bypass, such as less systemic inflammatory response, haemolysis, and high transfusion requirements because of the decreased surface, some aspects can lead to complications such as gaseous cerebral microemboli. With the optimised method, we hope to find a circulation system that combines the positive effects of both minimised and conventional cardiopulmonary bypass.”

Jennifer Taylor is a freelance medical journalist.
Spotlight: José Luis Lopez-Sendon, MD, PhD

Showing That a Lower Cooling Level May Be Associated With a Better Outcome in Patients Surviving Out-of-Hospital Cardiac Arrest Secondary to a Shockable Rhythm

José Luis Lopez, professor of cardiology, University La Paz, Madrid, Spain, and chief of cardiology, University Hospital La Paz, talks to Paula Hensler, MD.

José Luis Lopez-Sendon, MD, PhD, professor of cardiology, University La Paz, Madrid, Spain, and chief of cardiology, University Hospital La Paz, enjoys identifying problems and finding the solution, as shown by >500 peer-reviewed publications, including his recent article in Circulation titled “Hypothermia in Comatose Survivors From Out-of-hospital Cardiac Arrest: Pilot Trial Comparing 2 Levels of Target Temperature.” The article concluded that a lower cooling level may be associated with a better outcome in patients surviving out-of-hospital cardiac arrest secondary to a shockable rhythm.

Professor Lopez-Sendon says, “Taking care of patients after a cardiac arrest by cooling the patient (or the animal, initially) is not new. For 10 years, ice cubes and cool water were used. It was an archaic way, and it took a long time to cool and then warm up the patient. Suddenly, it was noticed that the lower the temperature, the higher the survival rates. Now, a machine is capable of pinpointing the temperature.”

The idea behind the study was to demonstrate this hypothesis and to reduce the mortality rate of cardiac arrest. Professor Lopez-Sendon continues, “We set up the randomised trial, which was approved by the ethics committee, filled in the paperwork, and prepared the study, which did not have many patients, and the results were impressive.”

He adds, “A larger study is needed. There is the open question of what happens to the heart rhythm when the patient is first attended and what the impact is on resuscitation. When there is ventricular fibrillation on the electrocardiogram, with advanced cardiocerebral resuscitation and advanced cooling, we get better results but need to demonstrate it. However, if there is asystole, we should abandon hope, and this has an impact on the family.

“Next, there is the issue of the optimal temperature target. What is it? 32°C to 34°C? Would lowering the temperature to 30°C give an extra advantage? The current data are not great; for the past 10 years the studies looked at temperatures <32°C. There are better cooling systems now.

“50 years ago, ventricular fibrillation was the first cause of death during acute myocardial infarction and was the force behind the new idea of an acute coronary unit; the patients at risk were grouped together in a unit with the new technology (ECG monitoring and defibrillators) and well-trained nurses. Today, ventricular fibrillation remains a major problem. Patients with cardiac arrest can be identified and properly resuscitated outside the hospital but a growing problem is irreversible cerebral damage after a prolonged cardiac arrest.”

Professor Lopez-Sendon and his group contribute to the multicentre international Global Registry of Acute Coronary Events (GRACE). “To belong to the GRACE core group is a life-time experience,” says Professor Lopez-Sendon. He and his team also enjoy being part of the Thrombolysis in Myocardial Infarction (TIMI) group, chaired by Marc Sabatine, MD, of the Brigham and Women’s Hospital, Boston, MA. The TIMI group is made up of “very open, science-focused people who understand clinical research,” says Professor Lopez-Sendon, and he describes Eugene Braunwald, MD, who set up the group and has become a close friend as “an extraordinary man.”

On Finishing His Residency, Professor Lopez-Sendon’s Father Gave Him a Subscription to Circulation

Professor Lopez-Sendon was born in La Palma, Canary Islands. He obtained his medical degree from the University of Valladolid, Valladolid, Spain, in 1973, and became a resident in cardiology in the same year. His father was a physician and inspired him to follow his path. In 1975, when Professor Lopez-Sendon finished his residency, his father gave him a subscription to Circulation. In 1978, Professor Lopez-Sendon was appointed as senior staff at the Hospital La Paz, and in 1993, he was appointed chief of the Coronary Care Unit at the University Hospital Gregorio Marañon, Madrid.

“My wife is also a cardiologist,” says Professor Lopez-Sendon. “We met at university and promised not to work together. I worked in the coronary care unit, and she worked in imaging and diagnostic technology, but she changed hospitals and now she is chief of the Echocardiography Lab in La Paz Hospital.” They have 2 children. Professor Lopez-Sendon is passionate about photography and scuba diving. He jokes, “If the Spanish medical system goes bust, I will open a scuba diving school.” Photo courtesy of Professor Lopez-Sendon.
While Professor Lopez-Sendon was training in cardiology, most doctors were going abroad to gain experience, and a number of Spanish doctors went to the National Institute of Cardiology, Mexico City, Mexico, which in the 1970s was at the forefront of cardiology. Professor Lopez-Sendon says, “At the time when coronary care units just started, cardiology was moving forwards in comparison with other specialties. I had the opportunity to work with doctors who returned from Mexico and were modern thinkers in cardiology, knew about targets, had methods for clinical research, and revolutionised clinical care.” One of these inspirational doctors was Jose Eizaguirre, MD, who organised the coronary care unit in Madrid and encouraged Professor Lopez-Sendon not to quit research and respect opinion.

Professor Lopez-Sendon believes that clinical research is part of clinical work. He says, “I have learnt to question everything, why something happens. An inquisitive mind is a good feature for research. The link between basic and clinical research is to try to answer something that can be relevant, what can you can and cannot do.”

Although Professor Lopez-Sendon did not pursue any training in the United States, he has developed long-term professional connections and friendships with physicians and researchers in the United States. One such person is Ann Bolger, MD, a cardiologist at San Francisco General Hospital, San Francisco, CA, and a member of the American Heart Association’s Council on Clinical Cardiology. Dr Bolger and Professor Lopez-Sendon first worked together on a training programme on heart failure in Spanish for Spanish-speaking doctors in the United States and South America. Professor Lopez-Sendon represented the Spanish Society of Cardiology and Dr Bolger, the American Heart Association. Together they built strong connections between the 2 societies and between the European Society of Cardiology and the American Heart Association. Professor Lopez-Sendon has been involved with the European Society of Cardiology for >20 years, participating in research projects as well as in continuous medical education activities, and has been a member of the board.

Professor Lopez-Sendon is involved in multicentre research projects and clinical trials that impact clinical practice. Probably the most relevant clinical research organised entirely at his hospital focussed on the diagnostic criteria for right ventricular infarction and cardiac rupture, 2 lethal conditions related to acute myocardial infarction.

Professor Lopez-Sendon is keen to carry out further clinical trials. “The issue,” he says, “is to convince everybody else that it is worth it and provide strong evidence. We need well-organised multicentre trials in hospitals in Spain and abroad. Funding is an issue. You need time for research and these are difficult economic times. In the past, you did not need much funding for research, but now the intervention, randomisation, paperwork, and follow-up are essential to provide research with quality controls, but it is cumbersome.”

Professor Lopez-Sendon’s philosophy is to gather the best people you can to build a team, and he says he learnt at the beginning of his career that you are measured by the people you are working with.

Reference

Contact details for Professor Lopez-Sendon: Cardiology Department, Hospital Universitario La Paz, Instituto de Investigación La Paz, Paseo de la Castellana 261, Planta 1, 28046 Madrid, Spain. Tel: +34 639 148 765. E-mail: jlopezsendon@gmail.com

Paula Hensler is a freelance medical writer.
European Meetings Update

23 June to 26 September, 2013

23 to 26 June
EHRA EUROPACE 2013
Athens, Greece
For further details, see http://www.escardio.org/congresses/ehra-europace-2013

23 to 26 June
EHRA EUROPACE 2013—37th EWGCCE
Athens, Greece
For further details, see http://www.escardio.org/congresses/ehra-europace-2013

26 to 29 June
ECSS Barcelona 2013—The 18th Annual Congress of the European College of Sport Science
Barcelona, Spain
For further details, see http://www.ecss-congress.eu/2013

27 to 27 June
ESC Webinar on the New Universal Definition of Myocardial Infarction
Online, France
For further details, see http://www.escardio.org/education/eLearning/webinars/general-cardiology

27 to 29 June
CSI 2013
Frankfurt, Germany
For further details, see http://www.csi-congress.org

6 to 7 July
17th Conference of the European Society for Clinical Hemorheology and Microcirculation
Pecs, Hungary
For further details, see http://www.eschm2013.hu/

7 to 10 August
40th International Congress on Electrocardiology
Glasgow, Scotland
For further details, see http://www.gla.ac.uk/colleges/mvlis/newsevents/ice2013

19 to 30 August
Cardiac Function in Health and Disease
Utrecht, the Netherlands
For further details, see http://www.utrechtsummerschool.nl

30 to 31 August
EHRA Case-based Arrhythmia and Device Course—Advanced Troubleshooting for Electrophysiologists
Amsterdam, the Netherlands
For further details, see http://www.escardio.org/education/live-events/courses/heart-rhythm/case-based-arrhythmia-device-course

31 August to 4 September
ESC Congress 2013
Amsterdam, the Netherlands
For further details, see http://www.escardio.org/congresses/esc-2013

1 to 6 September
Short Course on Prevention Strategies for Non-communicable Diseases
Oxford, United Kingdom
http://www.dph.ox.ac.uk/bhfhp/ncdshortcourse2013

15 to 17 September
PCR London Valves 2013
London, United Kingdom
For further details, see http://www.escardio.org/communities/EAPCI/congress-meetings/Pages/london-valves-2013

19 to 21 September
International Congress on Cardiovascular Technologies (Cardiotechnix 2013)
Algarve, Portugal
For further details, see http://www.cardiotechnix.org/

19 to 21 September
Exercise Rehabilitation and Long-Term Management of Heart Failure Patients
Bern, Switzerland
For further details, see http://www.escardio.org/communities/HFA/education

22 to 25 September
Computing in Cardiology 2013
Zaragoza, Spain
For further details, see http://www.cinc2013.org

25 to 27 September
14 ème Journées de Rythmologie 2013
Avignon, France
For further details, see http://www.sfcardio.fr/congres/congres-des-groupes/25-27-septembre-2013-14es-journees-de-rythmologie

25 to 25 September
How to Manage the NOACS in Clinical Practice, a Case-Based Approach
Online, France
For further details, see http://www.escardio.org/

26 to 29 September
3rd Dubrovnik Cardiology Highlights
Dubrovnik, Croatia
For further details, see http://www.escardio.org/education/live-events/courses/cardiology-update-dubrovnik

26 to 28 September
XVIIth International Congress of the Polish Cardiac Society
Wroclaw, Poland
For further details, contact http://www.ptkardio2013.pl/