Spotlight: John Pernow, MD, PhD, FESC

“Arginase Is a Key Mediator of Endothelial Dysfunction in Type 2 Diabetes Mellitus and Coronary Artery Disease, and Inhibition of Arginase Activity Markedly Improves Endothelial Function”

John Pernow, professor of cardiology and head, Academic Cardiology Unit and Cardiology Group Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden, and senior consultant in cardiology, Karolinska University Hospital, Stockholm, talks to Mark Nicholls.

As last author of a recent article in Circulation titled “Arginase Inhibition Improves Endothelial Function in Patients With Coronary Artery Disease and Type 2 Diabetes Mellitus,” John Pernow, MD, PhD, FESC, professor of cardiology and head, Academic Cardiology Unit and Cardiology Group Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden (see http://circ.ahajournals.org/content/117/18/f103), and senior consultant in cardiology, Karolinska University Hospital, Stockholm, says, “In a previous animal study, we showed that arginase is involved in microvascular dysfunction in rats with type 2 diabetes mellitus. We hypothesized that increased arginase activity may contribute to endothelial dysfunction in patients with type 2 diabetes mellitus and coronary artery disease.” To test this hypothesis, Professor Pernow and his colleagues investigated endothelial function before and after arginase inhibition in patients with type 2 diabetes mellitus and coronary artery disease, patients with coronary artery disease without diabetes mellitus, and healthy controls.

Professor Pernow says, “The main findings were that arginase inhibition improved endothelial function in patients with type 2 diabetes mellitus and coronary artery disease, patients with coronary artery disease without diabetes mellitus, and healthy controls.

“The beneficial effect of arginase inhibition on endothelial function was significantly greater among patients with diabetes mellitus in comparison with those without diabetes mellitus.

“This finding shows, for the first time, that arginase is a key mediator of endothelial dysfunction in patients with type 2 diabetes mellitus and coronary artery disease, and that inhibition of arginase activity markedly improves endothelial function among these patients.”

On other pages...

Funding: Austrian Society of Cardiology Research Scholarships
Recipients of Austrian Society of Cardiology Research Scholarships over the past 3 years describe the funding, their work groups, and their research.
Professor Pernow heads cardiology research at the Karolinska Institutet, where the scientific activity focuses on basic experimental research to patient-oriented trials. Research activities span the cardiovascular spectrum. Major contributions from the centre have focused on atherosclerosis, diabetes mellitus and cardiovascular disease, endothelial function, ischaemia reperfusion injury, women and heart disease, cardiac pacing and device treatment in heart failure, cardiovascular prevention, and invasive electrophysiology.

As well as the work that led to this recent Circulation article, Professor Pernow’s most enjoyable research includes demonstrating that endothelin receptor antagonists protect from myocardial ischaemia reperfusion injury in 1995; showing that endothelin receptor antagonists improve endothelial function in patients with coronary artery disease in 2002; finding that endothelin receptor blockade increases insulin sensitivity in patients with insulin resistance in 2007; and demonstrating that inhibition of arginase increases nitric oxide production and reduces infarct size in 2010. Professor Pernow explains, “These articles have been the most satisfying mainly due to their news value because they demonstrated novel effects of endothelin and arginase.”

Professor Pernow’s work is funded by the Swedish Research Council, Swedish Heart and Lung Foundation, Stockholm County Council, the Karolinska Institutet, and the European Association for the Study of Diabetes. He has won a number of special awards and prizes, including the Alvarengas prize from the Swedish Society of Medicine in 1998 and 2009.

Professor Pernow would like to see greater cohesion between clinical work and research and academic work at his hospital. “The academy and clinical organisations are parallel organisations with too little interaction,” he says. “This is mainly due to the lack of synergy between financial resources for research and flow of patients to university hospitals. At Karolinska University Hospital, we have >80% of resources for research in the Stockholm area but a minority of patients needed for our research projects. This is related to political decisions that do not give priority to the needs of patient volumes for clinical research.”

“A challenge is to try to influence the medical and academic structure in Stockholm towards an organisation that will harmonise patient volumes and high-quality clinical research.”

Demonstrating Novel Effects of Endothelin and Arginase

Professor Pernow was born in Stockholm in 1960 and started his medical education at the Karolinska Institutet in Stockholm in 1981. He took a break from medical school in 1984 to start his PhD in pharmacology, which created his additional interest in cardiovascular regulation, particularly during his PhD investigation of neuronal control of vascular function. He says that this period of his life was a time “full of joy and little responsibilities.”

After his PhD in 1988, Professor Pernow continued medical school and graduated in 1990. He did his internship at Nacka Hospital, Stockholm, from 1990 to 1991, and cardiology training at the Karolinska University Hospital from 1991 to 1997, including a postdoc clinical research position with the Swedish Research Council from 1992 to 1995 in the Department of Cardiology at Karolinska Hospital. He became a specialist in cardiology and internal medicine in 1997, associate professor in cardiology in 1998, and senior consultant in cardiology in 2001.

Professor Pernow says, “I became interested in cardiovascular physiology and pharmacology early on, so I started the PhD in pharmacology. I always had the ambition to become a clinician. It was therefore logical to continue to cardiology training after my PhD. My interest in vascular regulation has continued throughout my research career.”

From 2001 to 2002, Professor Pernow held a clinical research position in cardiovascular medicine with the Research and Development Committee of Karolinska
Hospital and a clinical research position with the Swedish Research Council from 2002 to 2008. He has been professor of cardiology since 2008 and combines the role with his responsibilities as a senior consultant in cardiology with clinical duties, which take up ≈30% of his time. The rest of his time is devoted to research, undergraduate and postgraduate teaching, and administrative work.

People who have helped shape Professor Pernow’s career include his tutor during his PhD, Professor Jan M. Lundberg, MD, PhD, who was a “great source of inspiration for science,” and his mentor during cardiology training and translation from basic science to clinical research, Professor Lars Ryden, MD, PhD (see http://circ.ahajournals.org/content/118/10/f55), the former head of the Department of Cardiology at Karolinska University Hospital. He received inspiration to attend medical school and conduct research from his father, Bengt Pernow, MD, who was professor of clinical physiology at the Karolinska Institutet. Other relatives involved in medicine have also proved influential, including his wife Ylva, an endocrinologist, his mother-in-law, Kerstin Hagenfeldt, who was a professor of obstetrics and gynaecology, and his father-in-law Lars Hagenfeldt, who was a professor of clinical chemistry.

Professor Pernow believes that ongoing research will help increase the understanding behind the development of atherosclerosis and vascular complications in diabetes mellitus. “Future developments will most probably be to prevent the development of these diseases and complications,” he comments.

“Another development will be the inhibition of reperfusion injury in acute myocardial infarction. Thanks to improved imaging techniques and carefully designed studies, knowledge gained in experimental studies will soon translate into positive clinical trials that will result in novel treatment strategies.” In addition, Professor Pernow looks forward to the development of imaging techniques that allow clinicians and researchers to visualise vulnerable atherosclerotic plaques noninvasively.

References

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Mark Nicholls is a freelance medical journalist.
Funding: Austrian Society of Cardiology Research Scholarships

Project-Related Scholarships Promote Cardiovascular Research in Austria and Personal Scholarships Create Long-Term Associations with Cardiology Departments and Societies in Other Countries

Recipients of Austrian Society of Cardiology Research Scholarships over the past 3 years describe the funding and their research to Jennifer Taylor, BSc, MSc, MPhil.

The Austrian Society of Cardiology awards scientific research scholarships each year. Project-related scholarships sponsor the development of cardiology in Austria and are awarded to institutions in Austria, which receive a maximum of €20,000 for 12 to 24 months. Most of the research must be performed in Austria. Personal scholarships are aimed at developing cardiology in the beneficiary’s home country and in Austria, and creating long-term associations with cardiology departments and societies in other countries. These scholarships are for up to €20,000 over 6 to 12 months, with a possible extension to 24 months. Austrians and foreigners with the corresponding qualification in Austria are eligible, and although there is no age limit, preference is given to applicants <40 year of age. Proof of previous research activities, written recommendations, and approval by the domestic or foreign institution are required. Mini projects that are part of an existing study in Austria but have no funding are also supported with up to €7000 for 6 to 12 months.

All applications should include a detailed research plan written by the project manager, an expected total budget for the research project, and a breakdown of costs. The scholarship funds personnel and materials but not lab equipment. Assurance should be provided that any outstanding funding requirements can be met by other sources.

The submission date for applications is 15 October each year. The grants are competitive, and an evaluation committee, chaired in 2013 and 2014 by Professor Otmar Pachinger, MD (see http://circ.ahajournals.org/content/121/17/f97), will rank all applications at the meeting of the board in January each year. Scholarships will be allocated during that meeting and can begin on 1 March at the earliest. Funds will be paid to the researcher’s institution.

Catharina Schreiber, MD, PhD student, Cardiovascular Biology PhD programme, Medical University Vienna, Vienna, Austria

Dr Schreiber received a project-related scholarship of €17,802 for the project “Sumoylation and Ubiquitination in a Rodent Model of Pulmonary Arterial Hypertension.” She is carrying out her research in the Department of Cardiology under the supervision of Professor Diana Bonderman, MD. Dr Schreiber says, “The primary objective of the study is to quantify SMAD proteins [transduce extracellular signals from transforming growth factor beta to activate downstream gene transcription] and specific enzymes involved in SMAD regulation in a rat model of pulmonary arterial hypertension.” SMADs play a major role in the integrity of the bone morphogenetic protein receptor type II pathway, and a defective pathway is highly associated with pulmonary arterial hypertension in humans. The group is also evaluating the treatment effects of a proteasomal inhibitor on intracellular SMAD protein levels and long-term haemodynamic parameters in the rat model.

Dr Schreiber with Professor Diana Bonderman and Magdalena Strobl, MD. Photo courtesy of Dr Schreiber.

Rayyan Hemetsberger, MD, physician, St. Johannes Hospital Dortmund, Dortmund, Germany

Dr Hemetsberger received a 12-month personal scholarship of €10,000 to conduct research at the Medical University of Vienna. In his study, mesenchymal stem cells were transfected with Luc-reporter gene and injected intracoronary or intramyocardially after closed chest reperfused myocardial infarction in pigs. In vitro bioluminescence...
imaging of mesenchymal stem cells indicated a higher degree of cell distribution in remote organs after intracoronal cell delivery and retention of the cells, mostly in the lymph nodes, bone marrow, and blood pool. Dr Hemetsberger says, “The underlying mechanism of migration to remote organs, whether active or passive, remains unclear.”

Matthias K. Freynhofer, MD, PhD student, Medical University of Vienna and resident, 3rd Medical Department, Cardiology, Wilhelminenhospital, Vienna, Austria

Dr Freynhofer received a project-related scholarship of €17,436 for 1 year for his PhD project “Wilhelminenhospital Monitoring of Antiplatelet Activity (WILMAA) Registry.” The research group is mainly supported by the Association for the Promotion of Scientific Research in the Area of Atherosclerosis, Thrombosis, and Vascular Biology (headed by Professor Kurt Huber, MD [see http://circ.ahajournals.org/content/123/10/f55], and Professor Johann Wojta, PhD; [see http://www.meduniwien.ac.at/atvb/co]). For the study, the group performed platelet function testing on consecutive patients undergoing percutaneous coronary intervention with stenting to predict clinical outcome and describe changes in the on-treatment platelet reactivity over time. “We showed that more precise standardisation of the vasodilator-stimulated phosphoprotein-phosphorylation assay in an in vivo mouse model of myocardial infarction. Their early results demonstrate that absence of intercellular adhesion molecule 1 results in less myocardial damage. They have also demonstrated that protein kinase C delta is essential for the cardioprotective effects of preconditioning. In a recent study, they showed that genetic disruption of phosphatidylinositol 3-kinase gamma exaggerates myocardial ischaemia/reperfusion. Professor Metzler says, “Using bone marrow-transplanted mice, we could demonstrate that the detrimental effect of phosphatidylinositol 3-kinase gamma loss was due to signalling within the cardiomyocytes.”

References

Bernhard Metzler, MD, professor and assistant medical director, Coronary Care Unit, Internal Medicine III/Cardiology, Innsbruck Medical University, Innsbruck, Austria

Professor Metzler received 6 project-related scholarships from 2005 to 2012. His working group mainly investigates inflammation and signal transduction in an in vivo mouse model of myocardial infarction. Their early results demonstrate that absence of intercellular adhesion molecule 1 results in less myocardial damage. They have also demonstrated that protein kinase C delta is essential for the cardioprotective effects of preconditioning. In a recent study, they showed that genetic disruption of phosphatidylinositol 3-kinase gamma exaggerates myocardial ischaemia/reperfusion. Professor Metzler says, “Using bone marrow-transplanted mice, we could demonstrate that the detrimental effect of phosphatidylinositol 3-kinase gamma loss was due to signalling within the cardiomyocytes.”

References

Noemi Pavo, MD, assistant physician, Department of Cardiology, Medical University of Vienna, Vienna, Austria

Dr Pavo received a 12-month personal scholarship of €17,200. Her research is ongoing in cooperation with Professor Joseph C. Wu, MD, PhD, Stanford School of Medicine, Stanford, CA. Previous work by their group indicated that percutaneous intramyocardial delivery of stem cells leads to an increase in myocardial hypoxia-inducible factor-1 alpha expression and a decrease in infarct size in an experimental model of closed chest reperfused myocardial infarction. Dr Pavo
Andreas Mangold, MD, resident physician in internal medicine and cardiology, Medical University of Vienna, Department of Internal Medicine II, Division of Cardiology, Vienna, Austria

Dr Mangold received project-related scholarships totalling €17456. He is a vascular biology PhD student working with the translational research team of Irene Lang, MD, professor of vascular biology at the Medical University of Vienna. Using the scholarship, he has characterised inflammatory cells in aspirates from the culprit lesion sites in ST-elevation acute coronary syndrome. “In our project, we have been investigating specific effector functions of primary polymorphonuclear leukocytes derived from the culprit lesion site of patients with ST-elevation acute coronary syndrome,” says Dr Mangold. “The in-depth characterisation of cellular mediators of plaque rupture should allow targeted approaches to prevent coronary occlusion.”

Jolanta Siller-Matula, MD, PhD, privat dozent, Department of Cardiology, Medical University of Vienna, Vienna, Austria

Dr Siller-Matula works with her coresearchers (Professors B. Jilma, I. Lang, G. Delle-Karth, and G. Christ) on the clinical pharmacology of antiplatelet drugs. Over the years they have demonstrated response variability to clopidogrel and aspirin; the link between high platelet reactivity to clopidogrel, genetic polymorphisms, and ischaemic risk in patients on dual antiplatelet therapy; the effect of drug interactions on the pharmacodynamics of antiplatelet drugs; and the impact of personalised antiplatelet treatment on clinical outcomes in patients with coronary heart disease.

Dr Siller-Matula says, “Our current research funded by a 24-month project-related scholarship of €18720 aims to characterise how various aspects of platelet function should be used to optimise treatment with novel platelet inhibitors.”

Paul Wexberg, MD, associate professor and cardiologist, 2nd Medical Department (head, Professor Franz Weidinger, MD), Rudolfstiftung Hospital, Vienna, Austria

Professor Wexberg was awarded a project-related scholarship of €15330. He says, “The aim of our study is to investigate the incidence of myocardial involvement in carriers of Duchenne muscular dystrophy and to assess the development of myocardial fibrosis (using late gadolinium enhancement and T1-mapping) and its association with left ventricular function and clinical condition over time.” Female carriers of Duchenne muscular dystrophy are often asymptomatic but can develop weakness of skeletal muscles and heart failure. Cardiac magnetic resonance can identify myocardial fibrosis, and may thus detect cardiomyopathies at an early stage.

Walter S. Speidl, MD, associate professor and medical consultant, Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria

Professor Speidl was awarded a 12-month project-related scholarship of €17866. Levosimendan is a positive inotrope for the treatment of acute decompensated heart failure. In clinical trials, it has proved effective, particularly for heart failure due to acute myocardial infarction. Professor Speidl says, “The aim of our study is to examine whether levosimendan has anti-inflammatory effects on human cardiac myocytes and human cardiac microvascular endothelial cells under hypoxic conditions in vitro, and may thereby prevent neutrophil recruitment that leads to myocardial damage during acute myocardial infarction in vivo.”

Jennifer Taylor is a freelance medical journalist.