Funding: The Estonian Science Foundation
Aiming to Encourage New Research Ideas, Support the Involvement of Young Researchers, and Develop International Cooperation

Cardiovascular researchers who have received funding from the Estonian Science Foundation describe the funding and their research to Jennifer Taylor, BSc, MSc, MPhil.

The Estonian Science Foundation awards grants for research projects in basic and applied research. Grants are for ≤4 years. Applicants (permanent residents of Estonia and citizens of other countries provided that their application is submitted through an Estonian institution) should have a doctoral degree from Estonia or an equivalent academic degree within the past 5 years and should have published a certain number and type of article. Grant holders should work in Estonia for ≥6 months of the year.

Investigating Induced Gene Expression in the Myocardium and the Inflammatory Response During Coronary Surgery (2010–2013)

Inga Karu, MD, PhD, researcher, Department of Anaesthesiology and Intensive Care, University of Tartu, Tartu, Estonia, and anaesthesiologist, 2nd Intensive Care Unit, North Estonian Medical Centre, Tallinn, Estonia, received funding from the Estonian Science Foundation for a project aimed at describing hyperoxia-induced changes in gene expression, activation of signalling pathways, and inflammatory response in the myocardium during both off-pump and conventional coronary surgery,1–3 and this will provide information to the ongoing debate about the matter,” she says. “We think that identifying changes in expression of multiple genes helps to detect whether signalling pathways that induce ischaemic preconditioning are activated by hyperoxia as well. If so, hyperoxic preconditioning can be easily used in clinical practice and may lead to an entirely new concept for the treatment of ischaemic heart disease.”

Short periods of myocardial ischaemia and reperfusion (ie, ischaemic preconditioning) are the most powerful protective phenomena against ischaemia-reperfusion injury in the heart. It has been demonstrated in animal studies that preischaemic hyperoxia elicits a similar protective effect in the myocardium. These experiments were performed by P. Tähepõld and A. Ruusalepp from the University of Tartu during their PhD studies at the Karolinska Institute, Stockholm, Sweden. The results of the pilot clinical study have been published.4

The research group is headed by Professor Joel Starkopf, MD, PhD, from the Department of Anaesthesiology and Intensive Care, University of Tartu, and the ongoing clinical study is based at 2 institutions: the University of Tartu with its Clinic of Anaesthesiology and Intensive Care and Department of Cardiac Surgery, and the Centre of Cardiothoracic Surgery and Clinic of Anaesthesiology of the North Estonia Medical Centre, Tallinn. Gene experiments will be conducted in collaboration with the Department of Physiology of the University of Tartu (Professor Sulev

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European Meetings Update, January 31 to February 21, 2013
List of cardiovascular meetings in Europe.
Köks, MD, PhD), and biochemical analyses are performed at the Institute of Biochemistry (Professor Mihkel Zilmer, MD, PhD), Centre of Excellence for Translational Medicine, University of Tartu.

References

**Investigating the Relationship Between Underlying Haemodynamic Abnormality and Antihypertensive Treatment in Patients With Arterial Hypertension (2010–2013)**

Prit Kampus, MD, PhD, senior research fellow, Department of Cardiology, University of Tartu, Tartu, Estonia, and cardiologist, Cardiology Centre, North Estonia Medical Centre Foundation, is using a grant from the Estonian Science Foundation to partially fund his main research project investigating the relationship between haemodynamic abnormalities in hypertension and their response to different classes of antihypertensive agents. The project’s team leaders are Professor Jaan Eha, MD, PhD (cardiology professor), and Professor Mihkel Zilmer, MD, PhD (biochemistry professor). Studies are coordinated and performed by Dr Kampus and Jaak Kals, MD, PhD (senior research fellow). Four cardiology residents and PhD students are also working on the project: Erik Salum, MD, is conducting the animal studies; and Martin Serg, MD, PhD, Maksim Zagura, MD, PhD, and Kaido Paapstel, MD, are assisting with the clinical studies.

The clinical study is a collaborative project with Ian Wilkinson, BMBCh, DM, and Carmel McEniery, PhD, from the Vascular Research Unit, University of Cambridge, Cambridge, England. The animal study is a collaborative study with Professor Alberto Avolio, PhD, and Mark Butlin, PhD, from Macquarie University, Sydney, Australia.

The goal of the clinical hypertension study is to determine the relationship between haemodynamic abnormalities (central and peripheral blood pressure, aortic stiffness, cardiac output, wave reflection, and peripheral resistance) in patients with hypertension and their response to different classes of antihypertensive agents. The group conducted a randomised, double-blind, placebo-controlled, crossover study in 80 male and female patients 18 to 80 years of age with essential hypertension. Patients received in random order 6-week treatments of bisoprolol, candesartan, doxazosin, modified-release isosorbide mononitrate, and placebo, and will be studied for 30 weeks. All measurements and blood tests are repeated at the end of each treatment phase.

For the animal study, the main aim is to study aortic stiffness and other haemodynamic parameters in a rodent model of diabetes mellitus with antihypertensive treatment. The specific aim is to investigate the potential protective effect of an angiotensin receptor blocker (telmisartan) on central haemodynamics throughout the blood pressure range in the diabetic rat. Arterial stiffness is measured via the femoral artery, and aortic pulse wave velocity is recorded over a mean arterial pressure range of 50 to 200 mm Hg using a dual pressure sensor catheter. Blood pressure will be acutely increased and decreased by an infusion of phenylephrine and sodium nitroprusside, respectively, via the intravenous line in the jugular vein.

Dr Kampus says, “The current project is closely linked to our previous projects for which, for the first time in Estonia, we carried out biochemical (using different biomarkers) and functional (endothelial function, arterial stiffness, central haemodynamic) assessments of arterial function by pulse wave analysis and pulse wave velocity in different disease models (ie, atherosclerosis, hypertension, diabetes mellitus, dermatitis atopicia) and investigated the effects of different drugs on central haemodynamics.” For this purpose, the first specialised scientific lab to carry out a functional-structural assessment of arteries—the Endothelial Centre—was established in Estonia within the Department of Cardiology, Department of Biochemistry, and Centre of Excellence for Translational Medicine at the University of Tartu. Four PhD theses have been defended successfully during the past 5 years under the guidance of the Endothelial Centre and the research team has established international scientific contacts among the universities of Tartu and Kuopio, Finland; Uppsala, Sweden; Cardiff, Wales; and Cambridge, England. The research team has demonstrated the association among subclinical inflammation, augmentation index, and central pulse pressure in healthy subjects and in hypertension and the effect of acute inflammation on vascular function.

“In 2007, I defended my PhD thesis titled ‘Impact of Inflammation, Oxidative Stress and Age on Arterial Stiffness and Carotid Artery Intima-Media Thickness’, says Dr Kampus. “I have participated in studies where we demonstrated impaired endothelial function in patients with peripheral arterial disease.” He adds, “Other studies have examined the effect of different inflammatory and oxidative stress biomarkers on arterial stiffness in different diseases (eg, peripheral arterial disease, diabetes mellitus, hypertension).”

From 2006 to 2009, Dr Kampus and his colleagues compared the effects of nebivolol versus metoprolol succinate...
on endothelial function and large artery stiffness during a 1-year period. They demonstrated that antihypertensive therapy with metoprolol succinate and nebivolol had similar effects on brachial blood pressure and arterial stiffness. Only nebivolol significantly reduced central blood pressure and reduced left ventricular wall thickness and reduced urinary 8-isoprostane levels and oxidised low-density lipoprotein independently of blood pressure reduction. “Our results demonstrate that the vasodilating beta-blocker, nebivolol, has superior effects on central blood pressure and reduction of target organ damage,” says Dr Kampus.

Animal studies carried out by Dr Kampus and his colleagues have shown that streptozotocin-induced diabetes mellitus impairs endothelial function and exerts differential effects on arterial stiffness in rats, characterised by increased aortic pulse wave velocity at supraphysiologically mean arterial pressure levels, whereas aortic elasticity was preserved at a lower pressure range. Dr Kampus says, “These results indicate that during the course of diabetes mellitus, early changes in arterial integrity are reflected in the increased central artery stiffness that can remain undetected because blood pressure may not be elevated at that stage. Increased arterial stiffness can be established when diabetic patients develop hypertension. This highlights the importance of adequate and early blood pressure control to prevent diabetic macrovascular complications.”

References

Elin Org (née Lühmussaar), PhD, senior scientist, Institute of Molecular and Cell Biology, University of Tartu, Tartu, Estonia, has currently moved to work as a postdoctoral fellow in the lab of Professor Aldons J. Lusis, PhD, at the University of California, Los Angeles, CA. Her grant from the Estonian Science Foundation has been used for cardiovascular research projects conducted in the Human Molecular Genetics research group headed by Professor Maris Laan, PhD, at the Institute of Molecular and Cell Biology. This 4-year project has also involved scientists Siim Söber, PhD, Katrin Kepp, PhD, and Gudrun Veldre, PhD, and doctoral students Margus Putku, MSc, and Peeter Juhanson, MSc.

The project was built on the results of a genome-wide association study for blood pressure traits conducted with the Helmholtz-Centrum in Munich, Germany. Dr Org says, “After a multistep replication study with European populations, we identified an association between the risk for hypertension and the CDH13 gene coding for T-cadherin, which functions as an adiponectin and low-density lipoprotein receptor.” Other studies have associated the same gene with various cancers and cardiometabolic and brain function. As a follow-up study, Dr Org and her colleagues aimed to identify genetic and epigenetic markers in the CDH13 gene responsible for pleiotropic functional effects. Dr Org explains, “We are currently investigating interindividual variation in the methylation status of a large number of CpG sites across the CDH13 promoter and gene body in order to explore the link between CpG methylation levels and a range of cardiovascular trait parameters.”

Professor Laan’s group has initiated the first genetic-epidemiological sample collection across Estonia to target essential hypertension (HYPEST, Hypertension in Estonia). With the support of the grant, the group has been able to collect additional information from selected families, and it recently published an article about the profile of Estonian patients with hypertension. The HYPEST sample has been used in several studies investigating the genetics of blood pressure and related traits, both in their own lab and in collaboration projects through memberships in large consortia (ie, Global Blood Pressure Genetics, the International Consortium for Blood Pressure Genome-Wide Association Studies, and the Global Urate Genomics Consortium).

Dr Org’s main research focus has been to determine the genetic component of cardiovascular diseases using both hypothesis-based (candidate gene) and hypothesis-free (genome-wide association studies) approaches. “This Estonian Science Foundation grant was the first research grant I have applied for as a principal investigator and it has allowed me to conduct high-level cardiovascular research in Estonia,” says Dr Org. “Our work has raised new scientific questions of broad interest to the scientific community.” Recently, Dr...
Org has expanded her research interests to investigate the role of gut microbiota in cardiometabolic phenotypes. Her current training in the Department of Cardiology, University of California Los Angeles is supported by the European Union through a Mobilitas Postdoctoral Research Grant and Marie Curie Fellowship.

References


Professor Björkegren in the lab. Photograph courtesy of Professor Björkegren.

Johan Lars Markus Björkegren, MD, PhD, MBA, professor of molecular pathology and group leader, Cardiovascular Genomics group, Department of Pathological Anatomy and Forensic Medicine, Tartu University Hospital, Tartu, Estonia, and associate professor of molecular medicine, Vascular Biology Unit, Department of Medical Biophysics and Biochemistry, Karolinska Institutet, Stockholm, Sweden, has worked at the 2 institutes since 2010. “The main goal of the 2 labs is shared,” says Professor Björkegren. “This is to investigate coronary artery disease using a systems medicine approach.” (Professor Björkegren was born in Sweden and is half Estonian. “My mother escaped Estonia with her family at the end of the World War II and eventually married my Swedish father,” he says. “This is the main reason that I started collaborating with scientists and clinicians in Estonia.”)

The lab in Tartu is responsible for several clinical biobanks, gathering DNA and RNA from as many of the disease-relevant organs in coronary artery disease as possible, including samples from diseased and healthy arterial wall, liver, skeletal muscle, and subcutaneous and abdominal fat. In addition, it gathers whole blood DNA from each study participant and conducts full clinical information and lab screens of blood samples. The focus is to gather clinical cohorts with genetics of gene expression data (mainly DNA and RNA). The genetics of gene expression datasets are used to infer regulatory and cross-tissue gene networks underlying key molecular processes of coronary artery disease and myocardial infarction, in particular, regulatory networks that are important in the cross-talk between organs.

“We foresee that molecular networks will provide the foundation on which preventive, predictive, and personalised cardiovascular care can be built,” Professor Björkegren says. “Besides providing clues to the most efficient targets for novel drugs, these networks will be essential for understanding the risk situation in any given individual.”

“At Tartu University, we also have a special focus on circulating monocytes and their role in coronary artery disease. In collaboration with the Centre of Translational Genomics, we aim to compare the reactivity of circulating monocytes from population-based controls gathered from the Estonian biobank with those in the coronary artery disease patients.” Professor Björkegren and his colleagues have set up cell model systems using cell lines for relevant cell types of coronary artery disease.

Professor Björkegren has funding from the Estonian Science Foundation and the Centre of Translational Genomics at the University of Tartu. His professorship is funded by the Archimedes Foundation in Estonia. The Estonian Science Foundation funding is being used for his lab in Tartu, which employs 4 to 5 PhD students/candidates, 1 technician, and 1 senior researcher. Professor Andres Metspalu, MD, PhD, at the Estonian Genome Centre of the University of Tartu and several other professors are associated with this centre. Professor Eric E. Schadt, PhD, Mount Sinai School of Medicine, New York, NY, is the main international collaborator. At the Karolinska Institutet, Professor Björkegren collaborates with several scientists, particularly vascular biologist based at the Department of Medical Biophysics and Biochemistry.

From earlier studies in humans, Professor Björkegren and his colleagues discovered 1 gene module/network strongly associated with the severity of coronary artery disease.² In this network, they also identified a novel key regulatory gene, the Lim domain binding-2 protein. From their studies in mouse models,³ they have examined and screened transcriptional activity at a genome level during...
progression of atherosclerosis, from the healthy artery to advanced states with widespread atherosclerotic lesions. Professor Björkegren says, “From these studies in mice and from a recent study on humans, we have learned that atherosclerotic lesions do not seem to grow linearly over a lifespan. Instead, they grow slowly for many years and reach a certain level or threshold at which the atherosclerotic plaque suddenly grows exponentially for 5 to 10 years in humans and 10 weeks in mice to reach some kind of saturation and again slower growth.”

Professor Björkegren concludes, “There is no doubt that my funding in Estonia plays a central role for my research goals. I hope to build a long-lasting collaboration between the Karolinska Institutet and the University of Tartu, particularly in the field of clinical genomics. I believe that establishing this collaboration will play an important role for my future career.”

References


Rein Raamat, PhD, senior researcher, Department of Physiology, University of Tartu, Tartu, Estonia, is using funding from the Estonian Science Foundation for a project aimed at developing a novel instrument and methodology for a beat-to-beat noninvasive blood pressure measurement using the radial artery. He says, “Applying this new radial measuring instrument and the previously constructed finger beat-to-beat noninvasive blood pressure monitor, it becomes possible to record and analyze the dynamic radial-to-finger pressure difference, which is known to contain valuable information on the autonomic nervous regulation of peripheral vascular tone.” Before this project, the research team developed an original technology, named servo-oscilometry or differential oscillometry, for continuous finger noninvasive blood pressure measurement.

Most of the work has been carried out in the Department of Physiology and the Institute of Exercise Biology and Physiotherapy, University of Tartu, in cooperation with Tartu University Hospital and their partners from Istanbul and Marmara Universities, Turkey.

The funding has been used to provide salaries for staff involved in research and development, scholarships for PhD students, foreign travel, equipment upgrade, materials and composites for manufacturing sensors and prototypes, and technological services.

To improve the accuracy of oscillometric noninvasive blood pressure measurement, a computer simulation study was carried out and demonstrated how several factors can induce errors. Various sensors were designed and optimised, and an experimental device for radial beat-to-beat blood pressure measurement was built and explored during the head-up tilt table tests in normal and high temperature environments. Comparison of the oscillometric beat-to-beat measuring device with invasive mean arterial blood pressure monitoring in intensive care patients showed good agreement between the noninvasive measurement and intra-arterial cannulation.

Applying the newly constructed radial beat-to-beat instrument together with the finger beat-to-beat monitor, the group recorded and analysed the dynamic radial-to-finger pressure gradient in healthy subjects during rest, light physical exercise, and local cooling. During intensive vasoconstrictions, the finger and radial monitors gave different responses; when the abrupt vasoconstriction was completed, the pressure signals became close again. Dr Raamat says, “In further development of this method, attention should be paid to proper positioning of the local pad-type cuffs to avoid overestimation of the radial pressure.”

References

Researching the Role of the Na+/Ca2+ Exchanger in Excitation-contraction Coupling and Energetics in Rainbow Trout Cardiomyocytes (2009–2012)

Rikke Birkedal, PhD, senior researcher, Institute of Cybernetics, Tallinn University of Technology, Tallinn, Estonia, works in the Laboratory of Systems Biology, an interdisciplinary lab combining biological science and computational modelling. The lab has 2 additional senior researchers (Marko Vendelin, PhD, and Pearu Peterson, PhD), 10 PhD students, and 2 MSc students. The Estonian Science Foundation funding is mainly used to pay stipends to 3 PhD students and 1 MSc student.

The project investigates the energetics of excitation-contraction coupling of rainbow trout cardiomyocytes. As cardiomyocytes are excited by an action potential, Ca2+ may enter the cytosol through L-type Ca2+ channels, reverse Na+/Ca2+-exchange, and Ca2+-induced Ca2+ release (CICR) from the sarcoplasmic reticulum. This leads to a transient increase in cytosolic Ca2+, which governs contractile force. In adult mammalian cardiomyocytes, CICR plays a dominant role in excitation-contraction coupling. In contrast, rainbow trout cardiomyocytes seem to depend mainly on Ca2+ influx from the extracellular space via L-type Ca2+ channels and reverse Na+/Ca2+ exchange. CICR may play a minor role that varies with temperature, heart rate, and adrenergic stimulation.

Dr Birkedal explains, “We use rainbow trout as a model animal to study whether this type of excitation-contraction coupling is energetically favourable. We use electrophysiology and fluorescence microscopy to quantify Ca2+ influx through the different pathways under varying physiological conditions.” She adds, “The next step is to record how this relates to oxygen consumption.” The project has generated 2 articles so far.1,2 Dr Birkedal concludes, “The current project is close to my heart because I use my background in both energetics and excitation-contraction coupling. I hope that our findings allow me to obtain funding in the future to continue this line of research.”

References

Jennifer Taylor is a freelance medical journalist.
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