

## European Perspectives

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# Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

## European Perspectives in Cardiology



## Funding: Latvian National Research Programme

### Opportunities for Scientific Institutions to Improve Their Scientific Capacity, Conduct Applied, Results-Oriented Research, and Develop Qualified Specialists for Further Scientific Activity

Recipients of Latvian National Research Programme funding describe the research funded by the grant to Jennifer Taylor, BSc, MSc, MPhil.

Latvia's National Research Programme is a major source of funding for cardiovascular research. In a given period, the state outlines priorities for scientific research in specific economic, educational, cultural, or other sectors. Priority scientific areas are approved by the Cabinet of Ministers and funded from the budget of the Ministry of Education and Science, Republic of Latvia. The aims and objectives of the programmes are determined by the ministries of the relevant sectors together with the Latvian Council of Science and the Latvian Academy of Sciences.

National research programmes provide opportunities for scientific institutions to improve their scientific capacity, conduct applied, results-oriented research, and develop qualified specialists for further scientific activity. The results of the programmes contribute to the development of intellectual capacity in Latvia and to the involvement of Latvian researchers in international projects.

Between 2005 and 2009, 9 national research programmes were commissioned, including 2 involving cardiovascular disease; between 2010 and 2013, 5 programmes were commissioned, including 1 involving cardiovascular disease.

#### New Medicinal Products and Means of Biocorrection: Design, Transport Forms, and Mechanisms of Their Action (2005 to 2009)

Professor Ivars Kalvins, PhD, director and head of the Department of Medicinal Chemistry, Latvian Institute of



Dr Dambrova in the lab. Photo courtesy of Dr Dambrova.

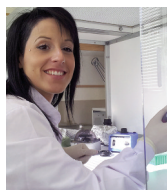
Organic Synthesis, Riga, Latvia, is the principal investigator of this programme to develop original approaches for the preparation of new medicines and diagnostics for the treatment of cardiovascular diseases.

Maija Dambrova, PhD, MBA, head, Lab of Pharmaceutical Pharmacology, Latvian Institute of Organic Synthesis, Riga, Latvia, received a research grant of €450 000 for 4 years under this programme to study the molecular mechanisms underlying pharmacological regulation of energy metabolism and discover novel targets for cardiovascular drugs. The grant provided financial support for basic research and covered the expenses for small equipment, lab materials, and salaries for researchers. She says, "With the funding, researchers investigated the effects of L-carnitine

#### On other pages...

**Funding: Luxembourg's National Research Fund Aides à la Formation-Recherche**  
Recipients describe the cardiovascular disease research funded by the grant.

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regulation in experimental models of cardiovascular diseases.” L-carnitine, a conditionally essential amino acid, is required for the transport of long-chain fatty acids into mitochondria for the generation of metabolic energy. Initial studies suggest that preconditioning-like manipulation of substrate metabolism through the regulation of L-carnitine homeostasis could be an effective approach for the prevention of myocardial infarction and the treatment of heart failure, especially for patients with type 2 diabetes mellitus.

The cardioprotective drug, mildronate, an inhibitor of L-carnitine biosynthesis and transport, was used to study the molecular consequences of L-carnitine regulation. Mildronate led to a decrease in the rate of carnitine palmitoyltransferase I-dependent fatty acid oxidation in mitochondria and, in turn, due to the Randle cycle, a substantial increase in the rate of basal and insulin-stimulated glucose uptake.<sup>1</sup> Enhanced glucose oxidation is beneficial during ischaemia because of the reduced proton production and less oxygen spent per adenosine triphosphate produced. Mildronate significantly reduced infarct size in an isolated rat heart infarction model, facilitated recovery from ischaemia-reperfusion injury,<sup>2,3</sup> and attenuated the development of atherosclerosis in an apolipoprotein E and low-density lipoprotein receptor double knockout mouse model.<sup>4</sup> It also decreased fed and fasted blood glucose concentrations and prevented diabetic complications in an experimental model of type 2 diabetes mellitus.<sup>5</sup>

Dr Dambrova says, “These findings indicate that a long-term decrease in L-carnitine availability induces compensatory mechanisms that alter the pathways of energy metabolism and is beneficial for the treatment of heart diseases and diabetes.”

### References

1. Liepinsh E, Vilskersts R, Loca D, Kirjanova O, Pugovichs O, Kalvinsh I, Dambrova M. Mildronate, an inhibitor of carnitine biosynthesis, induces an increase in gamma-butyrobetaine contents and cardioprotection in isolated rat heart infarction. *J Cardiovasc Pharmacol*. 2006;48:314–319.
2. Liepinsh E, Vilskersts R, Skapare E, Svalbe B, Kuka J, Cirule H, Pugovics O, Kalvinsh I, Dambrova M. Mildronate decreases carnitine availability and up-regulates glucose uptake and related gene expression in the mouse heart. *Life Sci*. 2008;83:613–619.
3. Liepinsh E, Vilskersts R, Zvejniece L, Svalbe B, Skapare E, Kuka J, Cirule H, Grinberga S, Kalvinsh I, Dambrova M. Protective effects of mildronate in an experimental model of type 2 diabetes in Goto-Kakizaki rats. *Br J Pharmacol*. 2009;157:1549–1556.
4. Vilskersts R, Liepinsh E, Kuka J, Cirule H, Veveris M, Kalvinsh I, Dambrova M. Myocardial infarct size-limiting and anti-arrhythmic effects of mildronate orotate in the rat heart. *Cardiovasc Drugs Ther*. 2009;23:281–288.
5. Vilskersts R, Liepinsh E, Mateuszuk L, Grinberga S, Kalvinsh I, Chlopicki, Dambrova M. Mildronate, a regulator of energy metabolism, reduces atherosclerosis in apoE/LDLR<sup>-/-</sup> mice. *Pharmacology*. 2009;83:287–293.

### Multidisciplinary Research Consortium on Main Pathologies Endangering Life Expectancy and Quality in the Latvian Population (2006 to 2009)

Professor Valdis Pīrāgs, MD, professor of medicine and head of the Department of Internal Medicine, Pauls Stradiņš Clinical University Hospital, University of Latvia, Riga, is the principal investigator of this programme. He says, “The aim of this programme was to create a multidisciplinary consortium involving medical faculties of 2 Latvian universities,



Professor Pīrāgs (left) and Professor Ērglis (right). Photo courtesy of Professor Pīrāgs.

3 university hospitals, and the main clinical and research institutions working in the field of medical research.”

The subprogramme “Elaboration of New Methods of Early Diagnostics, Prevention, and Treatment of Cardiovascular Diseases,” was led by Andrejs Ērglis, MD, PhD, professor, University of Latvia, director and leading researcher, Institute of Cardiology, and chief, Latvian Centre of Cardiology, Pauls Stradiņš Clinical University Hospital. It joined with 2 subprogrammes on cardiometabolic diseases, “Modern Approaches in Early Diagnostics, Prevention, and Treatment of Diabetes Mellitus and Obesity-Related Diseases,” led by Professor Peteris Tretjakovs, PhD, and “Prospective Follow-up Programme on Risk Factors and Clinical Forms of the Cardiometabolic Syndrome,” led by Professor Aivars Lejnicks, MD.

The cardiovascular research was divided into several parts. The first focused on creation of the Percutaneous Coronary Intervention Patient Registry and several invasive cardiology studies to optimise the percutaneous coronary intervention strategy for unprotected left main artery disease.<sup>1</sup> Collaborative studies with the Latvian Biomedical Research and Study Centre on genetic polymorphisms in genes coding for interleukin-6, cyclooxygenase-1, and purinergic 1 receptor implicated in the development of chronic total occlusions of coronary arteries, acute thrombus formation, and individual pharmacodynamic response to anticoagulant therapies resulted in 3 articles.<sup>2</sup> A randomised comparative study on the relation of soluble cytokines and inflammatory chemokines to insulin resistance and coronary artery disease was performed by the joint research groups.<sup>3</sup> A prospective follow-up survey on cardiometabolic risk prevention by researchers from the Riga Stradiņš University resulted in an article on blood pressure control in the daily practice of Latvian family physicians.<sup>4</sup>

Professor Pīrāgs concludes, “Funding from the National Research Programme also gave momentum to the first population-based cross-sectional study on cardiovascular risk factors in Latvia, which provided reliable information on the cardiovascular risk factor profile in adults.”<sup>5</sup>



## References

1. Narbutė I, Jegere S, Kumsars I, Mintale I, Zakke I, Bumeistere K, Sondore D, Grave A, Erglis A. Are paclitaxel-eluting stents better in unprotected left main coronary artery disease? Three-year clinical and intravascular imaging results from a randomized study. *Medicina (Kaunas)*. 2011;47:536–543.
2. Ignatovica V, Latkovskis G, Peculis R, Megnis K, Schioth HB, Vaivade I, Fridmanis D, Pirags V, Erglis A, Klovins J. Single nucleotide polymorphisms of the purinergic 1 receptor are not associated with myocardial infarction in a Latvian population. *Mol Biol Rep*. 2012;39:1917–1925.
3. Tretjakovs P, Jurka A, Bormane I, Mikelsone I, Elksne K, Krievina G, Reihmane D, Verbovenko J, Bahs G. Circulating adhesion molecules, matrix metalloproteinase-9, plasminogen activator inhibitor-1, and myeloperoxidase in coronary artery disease patients with stable and unstable angina. *Clinica Chimica Acta*. 2012;413:25–29.
4. Stukena I, Apanavičienė DA, Bahs G, Kalvelis A, Dzerve V, Ansmite B, Kalejs O, Lejnieks A. Blood pressure control in treated hypertensive patients in daily practice of Latvian family physicians. *Medicina (Kaunas)*. 2011;47:586–592.
5. Ērglis A, Dzēve V, Pahomova-Strautiņa J, Narbutė I, Jegere S, Mintāle I, Ligerė R, Apinis P, Lejnieks A, Misiņa D, Rozenbergs A. A population-based cross-sectional study of cardiovascular risk factors in Latvia. *Medicina (Kaunas)*. 2012;48:310–316.

### Development of New Preventive, Treatment, Diagnostic Means and Methods, Biomedical Technologies for Improvement of Public Health (2010 to 2013)

Professor Pīrāgs is the principal investigator of this programme, which has 3 clusters. Cluster 1 focuses on cardiovascular and metabolic diseases (leaders: Professor Ērglis and Professor Kalvins). Professor Ērglis says, “During the implementation of the last 2 national research programmes we have carried out research across close to the full spectrum of basic, translational, and practical cardiovascular medicine according to the funds available. We have conducted research at regional and national levels within the Nordic Baltic network, as well as at European and global levels.”

Cardiovascular disease is the leading cause of death in Latvia, and the first national population-based cross-sectional study showed a high prevalence of cardiovascular risk factors.<sup>1</sup> The mean number of risk factors was  $2.99 \pm 0.03$  per person: 75% participants had hypercholesterolemia, 45% were hypertensive, and 38% were overweight. Further longitudinal population-based studies are needed to estimate the interaction of different risk factors and the course of illness.

During the project, the researchers evaluated new diagnostic and treatment strategies. Recently, a noninvasive method for estimating computational fractional flow reserve, based on coronary computed tomography angiography, was introduced. The first-in-man studies with this technology were performed in 2009. Professor Ērglis says, “Findings from these studies<sup>2,3</sup> were important for defining the role of percutaneous coronary intervention in revascularisation guidelines. We have also significantly improved collaboration between cardiac surgeons and cardiologists, and our heart team can work on advanced hybrid procedures.”

Several studies have been performed to evaluate the association of different genetic polymorphisms with coronary artery disease in the Latvian population.<sup>4</sup>



Cardiovascular researchers working with Professor Ērglis on the National Research Programme projects. Photograph courtesy of Professor Ērglis.

Since 2008, ongoing clinical trials in Latvia have been involved in transplantation of autologous bone marrow mononuclear cells for patients with acute myocardial infarction, chronic heart failure (including paediatric dilated cardiomyopathy), and diabetes mellitus. The research team reported the efficacy and safety data on cell therapy for 7 patients with paediatric dilated cardiomyopathy.<sup>5</sup>

Professor Ērglis says, “Latvia would qualify for the award of the world’s most effective medicine. Despite having one of the lowest public health spends in the European Union (3.2% of GDP in 2012), Latvia has made significant progress in both clinical medicine and cardiovascular research. The morbidity and mortality from acute coronary syndrome, as well as total mortality from cardiovascular disease, have decreased over the past 5 years. Latvian medicine is like an open access establishment that provides high performance for relatively low costs.”

## References

1. Ērglis A, Dzēve V, Pahomova-Strautiņa J, Narbutė I, Jegere S, Mintāle I, Ligerė R, Apinis P, Lejnieks A, Misiņa D, Rozenbergs A. A population-based cross-sectional study of cardiovascular risk factor in Latvia. *Medicina (Kaunas)*. 2012;48:310–316.
2. Trusinskis K, Juhnevica D, Strenge K, Erglis A. iMap intravascular ultrasound evaluation of culprit and non-culprit lesions in patients with ST-elevation myocardial infarction. *Cardiovasc Revasc Med*. 2013;14:71–75.
3. Maeng M, Holm NR, Erglis A, Kumsars I, Niemelä M, Kervinen K, Jensen JS, Galløe A, Steigen TK, Wiseth R, Narbutė I, Gunnes P, Mannsverk J, Meyerdieks O, Rotevatn S, Nikus K, Vikman S, Ravkilde J, James S, Aarøe J, Ylitalo A, Helqvist S, Sjögren I, Thaysen P, Virtanen K, Puhakka M, Airaksinen J, Christiansen EH, Lassen JF, Thuesen L; Nordic-Baltic Percutaneous Coronary Intervention Study Group. Long-term results after simple versus complex stenting of coronary artery bifurcation lesions: Nordic Bifurcation Study 5-year follow-up results. *J Am Coll Cardiol*. 2013;62:30–34.
4. Ignatovica V, Latkovskis G, Peculis R, Megnis K, Schioth HB, Vaivade I, Fridmanis D, Pirags V, Erglis A, Klovins J. Single nucleotide polymorphisms of the purinergic 1 receptor are not associated with myocardial infarction in a Latvian population. *Mol Biol Rep*. 2012;39:1917–1925.
5. Bergmane I, Lacis A, Lubaua I, Jakobsons E, Erglis A. Follow-up of the patients after stem cell transplantation for pediatric dilated cardiomyopathy. *Pediatr Transplant*. 2013;17:266–270.

Jennifer Taylor is a freelance medical journalist.

# Funding: Luxembourg's National Research Fund Aides à la Formation-Recherche

Recipients of Luxembourg's National Research Fund Aides à la Formation-Recherche Grant Scheme for cardiovascular disease research describe the research funded by the grant to Jennifer Taylor, BSc, MSc, MPhil.

Luxembourg's National Research Fund offers the Aides à la Formation-Recherche Grant Scheme to support PhD and postdoctoral research training projects in Luxembourg and abroad. The scheme aims to develop human resources in Luxembourg research. It does this by improving the general working conditions and career perspectives of researchers through early access to work contracts and supplementary training opportunities. In its selection process, the Luxembourg National Research Fund looks favourably on high-quality proposals with a special focus on research training.

The Grant Scheme has no thematic or nationality restrictions. Applications are welcome from all researchers who wish to undergo research training in Luxembourg or abroad. In the selection process, the Luxembourg National Research Fund will consider how the project contributes to research and development in Luxembourg. PhD applicants should have a university degree. Grants are for 3 years with a possible extension of 1 year. Postdoctoral candidates must have received their PhD no more than 8 years previously. The postdoctoral training must be conducted in a country different to the one the applicant has been working in for the previous 24 months. Grants are for up to 2 years.

Project proposals for PhD and postdoctoral grants are assessed according to the scientific quality of the research project, the profile of the applicant, the quality of the host institution, and the interest of the research project in the Luxembourg research and development setting. Postdoctoral projects are also evaluated on their potential for career development. Judging is carried out by external experts in the subject field and applicants receive written feedback outlining how the funding decision was made.

## Investigating the Anti-inflammatory and Antioxidant Properties of Molecules That Specifically Target the Heme Oxygenase 1/Carbon Monoxide Pathway

Benjamin Haas, PhD, postdoctoral researcher, INSERM U955 Equipe 03, Laboratoire Physiopathologie et Pharmacologie des Insuffisances Coronaire et Cardiaque, Faculté de Médecine, Créteil, France, received a postdoctoral grant from 2012 to 2014 to conduct the project titled, "Heme Oxygenase 1 as Drug Target in Cardiovascular Inflammation: Mechanistic Studies, Translational and Systems Biology Approaches." The project is co-supervised by Roberto Motterlini, PhD, in France, an expert in the field of heme oxygenase 1 and carbon monoxide research, and Francisco Azuaje, PhD, in Luxembourg, a pioneer in systems biology approaches.



Dr Haas in the lab. Photograph courtesy of Benjamin Haas.

Dr Haas aims to characterise the contribution of a controlled heme oxygenase 1 induction in the setting of acute inflammation using *in vitro* models. Several cardiovascular pathologies are accompanied by an acute or a chronic inflammatory response in association with persistent oxidative stress. Cardiovascular inflammation is mediated by activation of the innate and adaptive immune system and can exacerbate tissue damage when deregulated, for example following a period of ischaemia. However, when ischaemia is counterbalanced, the return of oxygen to cardiovascular tissues during the reperfusion phase is known to generate reactive oxygen species, which can disrupt cellular membranes, oxidise structural and functional proteins, and lead to the recruitment of leukocytes, the principal mediators of the inflammatory response. Heme oxygenase 1 is a cytoprotective, stress-inducible enzyme that mediates the elimination of free heme. This reaction generates carbon monoxide, which is an important intracellular messenger in physiological and pathological mechanisms, including inflammation.

Dr Haas says, "We are particularly interested in studying the effects of carbon monoxide on inflammation and oxidative stress through the use of the metal carbonyl compounds that act as carbon monoxide-releasing molecules."

Differential and currently unknown targets of carbon monoxide are likely involved in the anti-inflammatory and protective actions mediated by heme oxygenase 1. Thus, identification of the major players in this response would help to better define the therapeutic potential of pharmacological agents targeting heme oxygenase 1. A systems biology approach, in which prototypical carbon monoxide-releasing molecules and heme oxygenase 1 inducers are



examined for their interaction with cellular networks, is also being investigated.

Dr Haas concludes, “This research will lead to a better understanding of the anti-inflammatory and antioxidant properties of molecules that specifically target the heme oxygenase 1/carbon monoxide pathway and will ultimately open opportunities for therapeutic drug development.”

### Investigating Whether Analogues of Adenosine With Receptor Specificities May Be Used to Inhibit the Development of Left Ventricular Remodelling After Myocardial Infarction

Jennifer Zangrando, MSc, PhD student, Lab of Cardiovascular Research, Centre de Recherche Public de la Santé, Luxembourg, received funding from 2012 to 2015 to conduct her PhD project titled, “Effects of Targeted Activation of Adenosine Receptors on Left Ventricular Remodelling Post Myocardial Infarction.”

Myocardial infarction can trigger the development of left ventricular remodelling, which can lead to heart failure. Currently, no medication exists to prevent the occurrence of left ventricular remodelling.

Adenosine is cardioprotective but its potential to inhibit left ventricular remodelling is unknown. Adenosine interacts with 4 receptors: A1, A2A, A2B, and A3. Each receptor has a particular pattern of expression and is coupled to specific signalling pathways.

Ms Zangrando says, “We previously observed that non-specific activation of all 4 receptors has a poor effect on left ventricular remodelling.”

The present project tests the hypothesis that activation, or inhibition, of specific adenosine receptors may prevent the development of left ventricular remodelling. To achieve this goal an experimental model of myocardial infarction induced by ligation of the left anterior descending coronary artery in mice is being studied. Left ventricular remodelling is assessed by positron emission tomography.

Ms Zangrando says, “Through this project we hope to find out whether analogues of adenosine with receptor specificities may be used to inhibit the development of left

ventricular remodelling after myocardial infarction. This research is important because left ventricular remodelling is an important determinant of prognosis after myocardial infarction. Being able to translate our basic findings to clinical application would improve the outcome of patients with myocardial infarction.”

### Investigating Whether Lymphangiogenesis Is Beneficial or Detrimental for Cardiac Repair

Bénédicte Lenoir, MSc, PhD student, Lab of Cardiovascular Research, Centre de Recherche Public de la Santé, Luxembourg, and the Lab of Tumor and Development Biology, GIGA Cancer, University of Liège, Liège, Belgium, received funding from 2010 to 2013 for her PhD project titled, “Effect of Adenosine on Angiogenic Signals Governing Left Ventricular Remodelling After Myocardial Infarction.”

Left ventricular remodelling leading to the development of heart failure is an important determinant of prognosis after myocardial infarction. The function of the lymphatic system in the heart is poorly characterised.

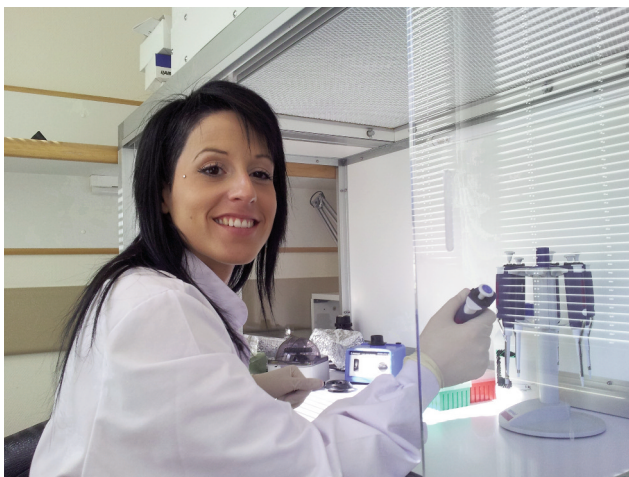
Recent studies suggest that the formation of lymphatic vessels from existing lymphatic vessels (lymphangiogenesis) may play a role in cardiac repair after myocardial infarction.

Adenosine is a cardioprotective nucleoside with proangiogenic properties. However, the effect of adenosine on lymphangiogenesis is unknown. In vitro, ex vivo, and in vivo experiments were undertaken to answer this question.

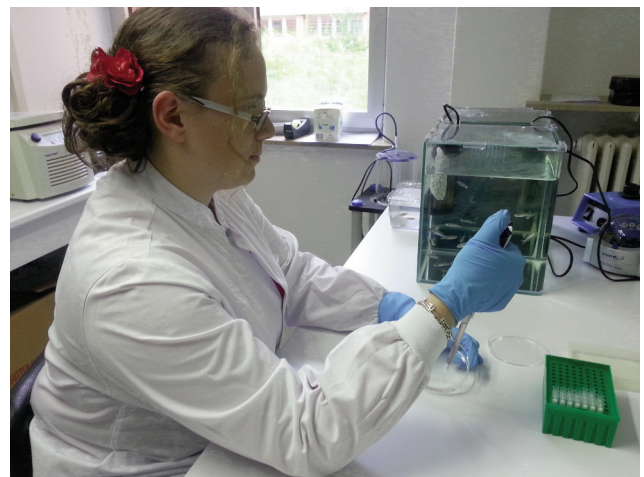
Through these experiments, Ms Lenoir and her colleagues hope to characterise the effect of adenosine on the growth and migration of lymphatic endothelial cells and the formation of lymphatic vessels in the heart.

Ms Lenoir says, “Ultimately, this project will show whether lymphangiogenesis is beneficial or detrimental for cardiac repair.”

“This research is important because it will increase our knowledge of the role of the lymphatic system in the diseased heart. It may also lead to the design of new therapies to treat myocardial infarction and heart failure.”



Jennifer Zangrando in the lab. Photo courtesy of Jennifer Zangrando.



Bénédicte Lenoir in the lab. Photo courtesy of Bénédicte Lenoir.

## Trying to Identify Genetic Factors and Biomarkers in Atherosclerosis



Thorben Kätzel in the lab.  
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du Luxembourg, 2013.

Thorben Kätzel, Master in Biology (Biochemistry), PhD student, Calcium Signalling and Inflammation group, Life Sciences Research Unit, University of Luxembourg, received funding from 2010 to 2014 for his PhD project titled “Stress- and Nutrition-Sensing Transcription Factors: Looking for Biomarkers in Atherosclerosis.”

Mr Kätzel says, “My project and research are part of a bigger medium throughput screening prospective study dealing with the possible interactions between stress mechanisms and their resulting inflammatory state and our lifelong exposure to micronutrients in the onset and development of atherosclerosis. Two mediators have been chosen to try to mimic these mechanisms in vitro: tumour necrosis factor- $\alpha$  as the cytokine responsible for cellular stress through its action, for example, on the transcription factor nuclear factor kappa-

light-chain-enhancer of activated B cells (NF- $\kappa$ B) signalling; and the micronutrient vitamin D (1,25-dihydroxyvitamin D3) acting on its nuclear receptor vitamin D receptor.”

Mr Kätzel’s project, composed of 2 complementary aspects—wet lab experiments and subsequent bioinformatics or systems biology analyses of the data, is supervised by Jean-Luc Bueb, PharmD, PhD, biology professor, Calcium Signalling and Inflammation Group, and Thomas Sauter, PhD, systems biology professor, Systems Biology Group, Life Sciences Research Unit.

Mr Kätzel says, “A crucial step in the development of atherosclerosis is the passage of monocytes from the injured vascular lumen to the extravascular tissue. A part of my wet lab functional experiments consisted of in vitro invasion assays to identify the influence of the previously identified and selected genes on the invading capabilities of treated monocytic cell line THP-1 into a complex synthetic gelatinous membrane model.”

Additionally, gene expression profile data processed from the microarrays, database knowledge, and literature knowledge is used to generate Boolean Network Models. Due to the availability of data sources, these models are often nonspecific and involve unnecessary interactions. A newly developed algorithm is used to reduce these models to smaller, more predictive models based on previously generated gene expression data. Ideally, this tool enables fast

generation of small Boolean Network Models specific to the desired research area. Mr Kätzel says, “This work, enabling in the complete described setup the analysis of crosstalks between NF- $\kappa$ B and vitamin D receptor signalling can then be easily transposed in endothelial cells in the frame of our prospective study, trying to identify genetic factors and biomarkers in atherosclerosis, but could also be applied to other pathologies.”

## Studying miRNA and Their mRNA Target Expression Patterns in Lean and Obese Spontaneously Hypertensive Heart Failure Rats



Gina Youcef in the lab.  
Photograph courtesy of  
Gina Youcef.

Gina Youcef, PhD student, Genomics Research Unit, Centre de Recherche Public de la Santé, Luxembourg, and INSERM Unit U1116, France, received funding from 2011 to 2014 for her PhD project titled, “MiRNA Profiling in the Progression From Hypertension to Heart Failure in the Context of a Metabolic Syndrome.”

Novel biomarkers with incremental values are required to guide diagnosis and therapeutic intervention. Small non-coding RNAs (miRNAs) are attractive candidates that have been shown to accurately reflect and predict many pathological states, including cardiovascular diseases.

Ms Youcef says, “Our project aims to study the miRNA and their mRNA target expression patterns in lean and obese spontaneously hypertensive heart failure rats that systematically develop heart failure in association or not with a metabolic syndrome. Profiling the transcriptome and miRNome in blood plasma and visceral adipose tissue specimens collected in these animals during the progression from metabolic syndrome to heart failure should allow us to identify disease stage-specific miRNAs and mRNAs that may later be used for diagnostic or therapeutic purposes.”

The study is part of an international project established between Laurent Vallar, PhD, at Centre de Recherche Public de la Santé, and Anne Pizard, PhD, at INSERM in France. miRNA/mRNA biomarker candidates identified in rats will be validated later in a translational study using human samples provided by the Clinical Investigation Centre in France within the context of 2 European Union FP7 programmes coordinated by Professor Faiez Zannad, MD, PhD (see <http://circ.ahajournals.org/content/118/21/f121>).

Jennifer Taylor is a freelance medical journalist.

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