Awards: The Belgian Society of Cardiology Young Investigator Award

Aiming to Encourage Young Physicians and Research Fellows

Recipients of the Belgian Society of Cardiology Young Investigator Award describe the research that led to their award to Jennifer Taylor, BSc, MSc, MPhil.

The annual Belgian Society of Cardiology Young Investigator Award of €6500 for investigators <35 years of age recognises basic and clinical research that is original and unpublished and has been performed in a Belgian institution. It aims to encourage young physicians and research fellows. The focus each year alternates between clinical and basic research. Applicants submit a 1-page abstract and a 3- to 5-page scientific article describing their aims, methods, and results. The board of the Belgian Society of Cardiology (see http://circ.ahajournals.org/content/116/25/F145) reviews the entries and accepts 3 abstracts for a 15-minute presentation at the Belgian Society of Cardiology annual meeting, followed by a formal discussion. Articles are judged on innovation, originality, scientific merit, and relevance.

2011: MicroRNA-146a: A New Kid on the Block in the Pathophysiology of Cardiac Hypertension and an Interesting Therapeutic Target

In 2012, Ward Heggermont, MD, PhD student, Center for Molecular and Vascular Biology, Division of Clinical Cardiology, University Hospitals Leuven, Catholic University of Leuven, Leuven, Belgium (see http://circ.ahajournals.org/content/118/12/F67), received the Young Investigator Award for his basic research on the role of microRNA-146a in cardiovascular disease, particularly in cardiac hypertrophy on pressure overload. “We investigated this microRNA in an in vivo murine model of pressure overload and are now trying to unravel the mechanism of

Dr Heggermont (4th right) with his colleagues of the joint Maastricht and Leuven labs. Photograph courtesy of Dr Heggermont.
action in vitro and at a subcellular level,” he says. “This is still a work in progress that we hope to publish in the upcoming year.”

Dr Heggermont graduated as an MD in 2009 from the University of Leuven and is a trainee in the Clinical Cardiology Department under the supervision of Professor Stefan Janssens, MD, PhD (see http://circ.ahajournals.org/content/119/21/f121). Since October 2010, he has been working on a PhD at the Center for Molecular and Vascular Biology funded by a personal research grant from the Flanders Research Foundation. His promoter is Professor Frans Van de Werf, MD, PhD (see http://circ.ahajournals.org/content/117/1/f1).

The lab consists of 2 research groups, one in Leuven and one in Maastricht, The Netherlands, both directed by his copromoter Professor Stephane Heymans, MD, PhD. The group mainly focuses on the process of inflammation in cardiovascular disease and its mediation by microRNAs and matricellular proteins. Anna-Pia Papageorgiou, PhD, works as a postdoc in the Leuven lab with Dr Heggermont. He says, “Currently, besides the implication of microRNA-146a in cardiovascular disease, I am also working on other microRNAs that are involved in inflammation, especially in viral myocarditis. This potentially life-threatening disease gives me the opportunity to pursue my personal interests in virology and cardiology.” From 2005 to 2007, Dr Heggermont worked as a student researcher in the Rega Institute, Leuven, which is recognised for its antiviral research. There he focused on a more fundamental research project aiming to unravel the role of certain proteins of coxsackie virus B3, one of the causative agents of myocarditis. Dr Heggermont says, “At that time, I learned to appreciate viruses as intriguing pathogens.” He concludes, “I above all want to thank all my colleagues in the lab for providing a nice work environment, which is a crucial factor for performing good research as a PhD student. I sincerely hope to continue on this path.”

References

2010: Iron Deficiency in Patients with Eisenmenger’s Syndrome: Does It Affect Outcome, Is Oral Anticoagulation Involved, and Can There Be too Much of a Good Thing?
Alexander Van De Bruaene, MD, PhD, cardiology registrar, University Hospitals Leuven, Belgium, received the 2010 Young Investigator Award for his work on the importance of iron.
of iron deficiency in patients with Eisenmenger’s syndrome. At the time, he was working under the supervision of Professor Werner Budts, MD, PhD, head of the Department of Structural and Congenital Heart Disease, University Hospitals Leuven.

In Eisenmenger’s syndrome, persistent venous to arterial mixing at the atrial, ventricular, or arterial level results in chronic hypoxaemia. Reduced tissue oxygenation causes a physiological increase in erythropoietin production, resulting in secondary erythrocytosis and increased oxygen carrying capacity. Sufficient iron stores are required to increase haemoglobin levels (and oxygen carrying capacity) and to stimulate adequate erythropoiesis, but up to one-third of patients with Eisenmenger’s syndrome are iron deficient.

Dr Van De Bruaene aimed to evaluate the importance of iron deficiency on the outcome, using the data of patients with Eisenmenger’s syndrome included in the Belgian Congenital Heart Disease Registry. The patients were followed prospectively. Data acquisition, analysis, and interpretation required collaboration with different academic centres in Belgium.

“Our results confirmed that iron deficiency was independently related with adverse outcome in patients with Eisenmenger’s syndrome,” he says. “There was also a relation between iron deficiency and the use of oral anticoagulation, suggesting that the risk should be taken into account when using oral anticoagulation in these patients.”

Currently, the group is trying to provide a framework for a goal-oriented treatment strategy in patients with Eisenmenger’s syndrome. In parallel, they have evaluated right ventricular function and pulmonary circulation at rest and during exercise in patients with an atrial septal defect type secundum using echocardiography at rest and during exercise. They found that patients who underwent late atrial septal defect closure present with a steeper pressure-flow plot compared with controls and those who underwent early closure.

Dr Van De Bruaene says, “As the right ventricle is able to tolerate volume load well for a long period of time, but poorly tolerates pressure load, this may have a negative impact on right ventricular function. A more precise evaluation of exercise physiology may be possible in the near future with studies involving exercise cardiac magnetic resonance imaging using a protocol developed by Professor Hein Heidbüchel, MD, PhD, Professor Marc Gewillig, MD, PhD, and Dr Andre La Gerche, MD, PhD.”

References

2009: Impaired Elastin Function Promotes Features of Plaque Instability in ApoE-Deficient Mice

Jozef L. Van Herck, MD, PhD, cardiologist, fellow in intensive care, Antwerp University Hospital, and the Laboratory of Pharmacology, University of Antwerp, under the supervision of Professor Christiaan J. Vrints, MD, PhD, and Professor Arnold G. Herman, MD, PhD. Previous studies from our group and other groups showed that changes in plaque composition are involved in plaque destabilisation. In addition to these intimal processes, important changes also occur in the media, including fragmentation of the elastic fibres and medial atrophy, which lead to an increase in arterial stiffness. In our study, we hypothesised that arterial stiffness is not only the consequence of atherosclerosis, but that it also contributes to its progression. Therefore, ApoE−/− mice were cross-bred with mice containing a heterozygous mutation—C1039G+/−—in the fibrillin-1 gene. Mutations in this gene lead to Marfan syndrome, which is characterised by fragmentation of elastic fibres and increased arterial stiffness. The results showed that arterial stiffness increased more rapidly in ApoE−/−C1039G+/− mice in the presence of atherosclerotic plaques. Arterial stiffness also promoted the development of larger and more unstable plaques in these mice.

“These findings indicate that there is a bidirectional interaction between atherosclerosis and arterial stiffness: arterial stiffness enhances the progression of atherosclerosis, which in turn accelerates arterial stiffening,” says Dr Van Herck. “One of the factors in this vicious circle is the pulse pressure. Arterial stiffening in ApoE−/−C1039G+/− mice was associated with an increased pulse pressure, which promoted plaque progression and instability through multiple pathways, including increased apoptosis of smooth muscle cells.”

Future research will evaluate whether inhibition of arterial stiffening is a promising therapeutic target to improve the prognosis of patients with increased cardiovascular risk.

Reference
2008: Circulating Adiponectin Levels in Patients with Chronic Heart Failure: The Effect of Exercise Training

An Van Berendoncks, MD, PhD, resident in cardiology, Antwerp University Hospital and postdoctoral fellow, University of Antwerp, received the 2008 Young Investigator Award for clinical research for her study on the effect of exercise training on circulating adiponectin levels in patients with chronic heart failure.

High circulating adiponectin levels are an independent risk factor of poor outcome in patients with chronic heart failure. The effect of 4 months of exercise training was studied in 46 patients with chronic heart failure, while 34 untrained patients with chronic heart failure served as a sedentary control group. Circulating adiponectin levels were significantly higher in patients with chronic heart failure compared with healthy subjects and increased with disease severity. Exercise training significantly reduced the levels in patients with chronic heart failure. In addition, adiponectin concentrations negatively correlated with exercise capacity, suggesting, but without firm evidence yet, that there might be a causal relationship.1

This project was part of Dr Van Berendoncks’ PhD thesis, and her supervisors were Professor Viviane Conraads, MD, PhD (see http://circ.ahajournals.org/content/122/12/167), and Professor Christiaan J. Vrints, MD, PhD. Patients with chronic heart failure were recruited from the Cardiac Rehabilitation Centre and the Heart Failure Clinic of Antwerp University Hospital, which involved close collaboration with Nadine Possemiers, RN, cardiac rehabilitation nurse, and Paul Beckers, PT, PhD, coordinator of the Cardiac Rehabilitation Centre. Biochemical analyses were performed at the Lab for Cellular and Molecular Cardiology, Antwerp University Hospital, with the help of Vicky Hoymans, MSc, PhD, head of the lab, and Geert Frederix, MSc, lab technician.

Dr Van Berendoncks says, “My PhD project investigated the role of adiponectin in chronic heart failure with a specific focus on skeletal muscle metabolism and the effect of exercise training.” First, the prognostic impact of adiponectin in relation to other clinical, lab, and exercise data was investigated.2 Second, the possible modulation of adiponectin levels by physical training was investigated. One of the most intriguing parts was to explore underlying pathophysiological mechanisms for the increased adiponectin concentrations in chronic heart failure, which included the investigation of local adiponectin expression and the downstream pathway at the level of the skeletal muscle.3 Finally, the group investigated the effect of exercise training on metabolic gene expression at the level of the skeletal muscle.4 Dr Van Berendoncks says, “For the final 2 studies, a great collaboration was started with Professor Renée Ventura-Clapier, PhD, Professor Anne Garnier, PhD, and Dominique Fortin of INSERM U769, University of Paris, Paris, France.”

As a result of presenting different parts of her PhD project, Dr Van Berendoncks won a poster prize for best presentation at the Belgische Vereniging voor Inwendige Geneeskunde—Société Belge de Médecine Interne Congress, Brussels, Belgium, in December 2009, a 2010 Heart Failure Association grant, and a poster prize for the best original scientific work in its category (prevention and epidemiology) at EuroPRevent, April 2011, Geneva, Switzerland.

Dr Van Berendoncks is continuing her residency in cardiology at Antwerp University Hospital and is investigating the hypothesis that elevated adiponectin levels are a marker of wasting in chronic heart failure, as well as the underlying mechanisms that may help elucidate the concept of “adiponectin resistance.” The group has initiated primary cultures of human skeletal muscle cells from satellite cells of skeletal muscle biopsies to allow further in vitro exploration of the adiponectin pathway in chronic heart failure.

Before specialising in cardiology, Dr Van Berendoncks performed research in the Nephrology Department, which was awarded a travel grant for best abstracts presented by young authors at the European Renal Association—European Dialysis and Transplant Association Congress in Glasgow, Scotland in July 2006.

References


Pieter-Jan Guns, PhD, Pharm D, research and innovation manager for Expert Group Antwerp Molecular Imaging, University of Antwerp, became fascinated in basic pharmacology research during a lecture by Professor Hidde Bult, PhD. Two years later, he started PhD research in his lab at the Division of Pharmacology, University of Antwerp. During his PhD, Dr Guns studied the role of purinergic receptors during atherosclerosis in apoE<sup>−/−</sup> mice. Initially, purinergic receptors on endothelial cells were characterised functionally by applying traditional pharmacological tools combined with the use of knockout mice.<sup>1</sup>

Furthermore, it appeared that apoE<sup>−/−</sup> mice with established atherosclerosis displayed decreased endothelium-dependent relaxation. Dr Guns says, “This endothelium dysfunction was thought to be caused by a reduced bioavailability of nitric oxide related to increased oxidative stress in atherosclerotic blood vessels.” To study this hypothesis, paraoxonase 1, a high-density lipoprotein-associated enzyme with antioxidative activity, was transiently overexpressed in apoE<sup>−/−</sup> mice with established plaques. Paraoxonase 1 overexpression decreased oxidative stress (oxidised low-density lipoprotein) and significantly improved endothelial function. The latter was independent of effects on plaque size, thereby demonstrating the beneficial potential of antioxidative interventions.<sup>2</sup> Dr Guns received the 2007 Young Investigator Award for basic research for this study.

After completing his PhD thesis, Dr Guns enrolled in cardiovascular safety pharmacology training and learned about screening for drug-induced prolongation of ventricular repolarisation, a surrogate risk marker for the development of arrhythmias (including torsade de pointes). After 3 years in safety pharmacology, he became involved in the startup company Bio-Plus Safety Pharmacology, a small contract research organisation dedicated to evaluating cardiovascular drug candidates in a guinea-pig platform.<sup>3</sup>

During this period he developed and validated a new risk marker for torsade de pointes arrhythmias: the electromechanical window, which combines electrical (QT interval) and mechanical (QLVPend) information into one superior risk marker.<sup>4</sup> “However,” says Dr Guns, “we didn’t succeed in turning these scientific innovations into business, partly due to the conservative nature of safety pharmacology and the tight budgets the pharmaceutical industry is facing.”

Dr Guns has since returned to the University of Antwerp as research and innovation manager for Expert Group Antwerp Molecular Imaging, the university’s imaging consortium, which focuses mainly on neuroimaging and oncology research. “Within this role, I can combine the best of both worlds,” he says. “Within the academic setting, I enjoy being close to ambitious fundamental research projects, whereas in collaborative projects with the pharmaceutical industry, I feel we are directly contributing to drug development and improvement of healthcare.”

References

2006: Multilevel Study of the Pathogenic Mechanisms Underlying Long QT Syndrome

Johan B. Saenen, MD, PhD, cardiologist, Antwerp University Hospital, received the Young Investigator Award for clinical research for a study on the biophysical characterisation of a c.1039 C>T (p.Pro347Ser) missense mutation in the hERG (human ether-a-go-go-related gene) potassium channel that is responsible for the rapid delayed rectifier current (I_Kr), which contributes to the repolarisation phase of the cardiac action potential.

A loss of I_Kr current has been implicated in type-2 long QT syndrome (LQTS), which predisposes to life-threatening arrhythmias. Both hereditary (cLQTS) and acquired (aLQTS) subtypes have been identified. However, cardiac ion channel disease (channelopathies) is notorious for its variable clinical expressivity, even among family members carrying the same mutation, with some remaining asymptomatic and others symptomatic at a young age.

“The p.Pro347Ser substitution raised our interest because it was found to be responsible for 2 distinct phenotypic LQTS expression forms,” says Dr Saenen. “We identified this genetic variant in a symptomatic LQTS family that displayed substantial clinical heterogeneity ranging from asymptomatic to QTc prolongation to sudden cardiac death.” The expressivity of the p.Pro347Ser variant suggested a typical cLQTS, favouring a pathogenic mutation.

The same p.Pro347Ser variant was found in an unrelated elderly patient who had never displayed LQTS-related traits or symptoms while taking a daily dose of cisapride, but the administration of 3 additional QT-prolonging drugs reverted it into a full-blown phenotype with QTc prolongation and episodes of torsade de pointes. The arrhythmogenic phenotype was fully reversible upon cessation of these compounds. The expressivity of this p.Pro347Ser variant is clearly an aLQTS phenotype. This finding suggests that the p.Pro347Ser variant is a bystander polymorphism because the patient had never shown any LQTS traits when taking a well-known QT-prolonging agent every day. In both cases, other genetic variants in LQTS1-3 and LQTS5-6 genes were excluded. The aims of the study were to establish the biophysical impact of the p.Pro347Ser variant on hERG ion channel function, to assess its effect at the action potential level, and to provide insight into how 1 mutation can give rise to such heterogeneous clinical expressivity. Therefore, by using a high-resolution patch-clamp approach and by integration of the in vitro biophysical properties into an action potential model, the group aimed to contribute to the knowledge on genotype–phenotype correlation by providing translational data.

The biophysical characterisation of the p.Pro347Ser potassium channels revealed a novel pathogenic mechanism of reciprocal changes in the inactivation kinetics combined with a dominant-negative reduction of the functional expression in the heterozygous situation.1

“Our data showed that these discrete biophysical changes were sufficient to prolong the action potential duration by approximately 10%, harbouring the pathogenic potential of overt LQTS,” says Dr Saenen. “We reasoned that, in the context of the multifactorial aetiology underlying LQTS, a modest reduction of the repolarising power can give rise to a spectrum of phenotypes originating from 1 mutation as the relative contribution of other factors that interplay in determining the threshold between clinical and subclinical phenotypes (eg, other genes involved in action potential generation, modifier genes) is more pronounced.”

He adds, “In contrast to previously reported severe overt phenotypes (ie, caused by pore-region or compound mutations), this ambiguous genetic variant brought about by discrete biophysical alterations in our view was exemplary to the unpredictable genotype–phenotype correlation displayed in many families with channelopathy. This analysis underscored the complexity of genotype–phenotype translation in more lenient manifestations of the disease and confirms the need for functional genetic analysis to overcome the hurdles of predicting the expressivity of the LQTS based on mere topology in the gene product and minor allele frequency.”

The study was carried out in the Lab for Molecular Biophysics, Physiology, and Pharmacology at the University of Antwerp and at the Cardiology Department, Antwerp University Hospital, under the guidance and supervision of Professor Dirk J. Snyders, MD, PhD, and Professor Christiaan J. Vrints, MD, PhD.

Dr Saenen concludes, “Currently this research unit has become part of a larger multidisciplinary cardiogenetics consortium, of which I am one of the many coworkers. My interests lie in the study and dedicated management of sudden cardiac death syndromes, including cardiomyopathies, primary electrical disease, and thoracic aortic aneurysm.”

Reference

Jennifer Taylor is a freelance medical journalist.