Funding: The Dutch Heart Foundation Dr E. Dekker programme

Clinical and Nonclinical Fellowships to Stimulate the Personal Career of Outstanding Investigators and Attract Scientists to the Field of Cardiovascular Research in the Netherlands

Recipients of the 14 grants awarded by the Dutch Heart Foundation Dr E. Dekker programme in 2012 describe their research funded by the grant to Jennifer Taylor, BSc, MSc, MPhil.

The Dutch Heart Foundation Dr E. Dekker programme, which began in 1987, provides grants for talented cardiovascular researchers at different stages in their scientific career. Dr E. Dekker was the medical director of the Dutch Heart Foundation from 1971 to 1987 and is credited with starting a programme in 1972 to train lay people to perform resuscitation. He also launched the publication of the brochure titled “Cardiovascular Disease in the Netherlands. Figures on Morbidity and Mortality.”

The aims of the programme are to stimulate the personal career of outstanding investigators at all stages, attract scientists to the field of cardiovascular research, and support the formation of a well-trained pool of high-level cardiovascular researchers in the Netherlands.

Since 1999, the fellowships have been provided along 2 lines: clinical and nonclinical. Clinical fellowships are for physicians before specialty, physicians in specialty training, paediatric research fellows, junior staff members, and clinical established investigators. Nonclinical fellowships are for paediatric research fellows, junior postdoctoral fellows, senior postdoctoral fellows, and established investigators.

The senior postdoctoral fellowship (nonclinical) is a new addition to the programme in 2012. Applicants should be conducting research in the diagnosis and treatment of cardiovascular disease but not be registered or in training, as a medical specialist. They need sufficient research experience to build their group, and the research should be embedded into the research programmes of the proposed institute. The scholarship provides financial support for 2 years’ salary and for a 4-year PhD student project. In addition, recipients can apply for up to €9000 each year to cover expenses. The cost of attending conferences is not covered but can be claimed from the Dutch Heart Foundation Dr W. Stiggelbout programme.

Aiming to Provide Aetiological Insights Linking Prestroke Vascular Pathology with Post-Stroke Prognosis

Mohammad Arfan Ikram, MD, PhD, associate professor of neuroepidemiology, Departments of Epidemiology, Radiology, and Neurology, Erasmus MC, Rotterdam, the Netherlands, was awarded a junior postdoctoral fellowship of €200 000 for 4 years for the project titled “The Role of Prestroke Vascular Pathology in Long-Term Prognosis After Stroke.” His research aims to better understand factors related to long-term outcomes after stroke, ie, dementia, depression, and death.

Most research addressing long-term prognosis after stroke has focused on risk factors measured at the time of stroke or even some time later, so might be influenced by the stroke itself. The main novelty of this project is that it focuses on vascular pathology and risk factors that were present before the stroke. The project is embedded in the population-based Rotterdam Study, a longstanding cohort study investigating chronic disease in the elderly.

Dr Ikram says, “Results from this project will provide aetiological insights linking prestroke vascular pathology with post-stroke prognosis. Factors identified in this project may be used for future risk stratification and serve as targets for preventive and therapeutic interventions.”

Dr Ikram will collaborate with Professor Albert Hofman, MD, PhD, Professor Peter J. Koudstaal, MD, PhD, Meike W. Vernooij, MD, PhD, and Professor Henning Tiemeier, MD, PhD, all at the Erasmus MC.
Aiming to Improve Patient Selection for and Effectiveness of Cardiac Resynchronisation Therapy

Joost Lumens, PhD, assistant professor of medical engineering, Department of Biomedical Engineering, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, the Netherlands, was awarded a 4-year junior post-doctoral fellowship of €300000 for the project titled “Noninvasive Patient-Specific Cardiovascular Simulation to Optimise Diagnosis and Pacemaker Treatment of Heart Failure.” The aim of the study is to improve patient selection for and effectiveness of cardiac resynchronisation therapy using an integrative personalised computer simulation approach that synergistically combines various conventional noninvasive measurements on mechanical, haemodynamic, and electrical cardiac function. The patient-specific simulation algorithm will be developed using the well-established CircAdapt cardiovascular modelling platform (www.circadapt.org).

Dr Lumens says, “In a broad range of patients with dysynchronous heart failure, the proposed patient-specific simulation approach will reveal diagnostic information that is otherwise concealed and will enable quantitative prediction of response to cardiac resynchronisation therapy by simulation of prognosis after intended pacing protocols. This diagnostic and prognostic information will enable the clinician to improve patient selection for cardiac resynchronisation therapy and its effectiveness on a patient-specific basis using only conventional diagnostic measurements.”

The proposed multidisciplinary research will be carried out at the Faculty of Health, Medicine and Life Sciences at Maastricht University in close collaboration with researchers from Maastricht University (Tammo Delhaas, MD, PhD, professor of biomedical engineering and chair, Department of Biomedical Engineering, and Frits W. Prinzen, PhD, professor of physiology, see http://circ.ahajournals.org/content/126/18/f103), University of Pittsburgh Medical Center, Pittsburgh, PA (John Gorcsan III, MD, professor of medicine and director of echocardiography), and Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France (Sylvain Ploux, MD, clinical research fellow; Pierre Bordachar, MD, PhD, chair, Division of Cardiac Stimulation; and Michel Haïssaguerre, MD, professor of cardiology and chair, Department of Cardiac Electrophysiology and Stimulation (see http://circ.ahajournals.org/content/114/17/f165).

Investigating Arrhythmogeneity in Pathological and Physiological Cardiac Hypertrophy

Brian O. Bingen, MD, research fellow, Department of Cardiology, Heart Centre Leiden, Leiden University Medical Centre, Leiden, the Netherlands, received a physician before specialty fellowship of ≈€107000 for the project titled “Counteracting Cardiac Arrhythmias by Converting Pathological into Physiological Cardiac Hypertrophy Through Genetic Engineering: A Yin and Yang Story.”

In contrast to physiological hypertrophy, pathological cardiac hypertrophy is associated with a decrease in cardiac function and increase in ventricular arrhythmias. The mechanisms responsible for the differences between these 2 hypertrophic phenotypes in terms of arrhythmogeneity are not clear.

Dr Bingen says, “Pathological and physiological hypertrophy are caused by distinct signalling pathways by pathological or physiological stimuli, respectively. Activating the physiological signalling pathway for a pathological stimulus might be beneficial for the resulting hypertrophic phenotype.”

The project aims to investigate how pathological hypertrophy affects arrhythmogeneity in cardiac tissue, which factors associated with physiological hypertrophy can safely and efficiently convert pathological into physiological hypertrophy, and whether and how forced induction of physiological hypertrophy reduces the proarrhythmic potential of pathological hypertrophied myocardial tissue.

The research will be conducted at the Lab of Experimental Cardiology in Leiden. Dr Bingen says, “In this lab, different scientists and physicians have joined forces to study the origin of cardiac arrhythmias and to development novel treatment options.” Dr Bingen’s collaborators on the project are Daniël A. Pijnappels, PhD (scientific supervisor), Professor Martin J. Schalij, MD, PhD (tutor), Antoine A. F. de Vries, PhD, and Professor Katja Zeppenfeld, MD, PhD.

Investigating the Role of Haematopoietic Stem and Progenitor Cells and the Bone Marrow Niche in Atherogenesis

Tom Seijkens, MD, PhD student, Department of Medical Biochemistry, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands, received a physician before specialty fellowship of ≈€100000 for the project titled, “Hypercholesterolaemia-Induced Priming of Haematopoietic Stem and Progenitor Cells: a Critical Pathway in Atherosclerosis.” The way the mature immune system behaves is largely determined by the multilineage differentiation of haematopoietic stem and progenitor cells in the bone marrow. In atherosclerosis, hypercholesterolemia has been
shown to induce leukocytosis. However, how hypercholesterolaemia affects haematopoietic stem and progenitor cells and the bone marrow niche, and how this skews the immune system during atherogenesis, are unknown.

The project aims to investigate how hypercholesterolaemia affects the bone marrow niche; how haematopoietic stem and progenitor cells are affected by hypercholesterolaemia; and the role of hypercholesterolaemia-primed haematopoietic stem and progenitor cells and their offspring in atherogenesis.

Dr Seijkens says, “We expect to unravel the effects of hypercholesterolaemia on haematopoietic stem and progenitor cells and the bone marrow niche. We will characterise the mechanisms of hypercholesterolaemia-induced haematopoietic stem and progenitor cells priming and how this contributes to the development of atherosclerosis. We expect that hypercholesterolaemia-primed haematopoietic stem and progenitor cells differentiation is skewed towards proinflammatory myeloid cell types that promote atherogenesis. Inhibition of this proinflammatory differentiation pathway at the haematopoietic stem and progenitor cell level may reduce atherosclerosis.” The research is being supervised by Professor Esther Lutgens, MD, PhD (see http://circ.ahajournals.org/content/124/23/f133).

Looking for Novel Early Pathways Involved in the Onset and Progression of Heart Failure

Peter van der Meer, MD, PhD, cardiologist, University Medical Centre Groningen, Department of Cardiology, Groningen, the Netherlands, received a junior staff grant of €210,000 for the project titled “Induced Pluripotent Stem Cells as an In Vitro Model for Cardiomyopathy; Exploration of Novel Pathways.”

Heart failure survival rate is <50% over 5 years. Understanding early changes in particular may lead to novel treatment targets. For the project, cardiomyocytes will be derived from patients who have cardiomyopathy using patient-specific pluripotent induced stem cells. With this tool, Dr van der Meer and his colleagues can mimic heart failure “in a dish.”

Dr van der Meer says, “We hope to discover novel early pathways involved in the onset and progression of heart failure. Novel identified pathways will be further explored in clinical and preclinical studies.” The project is co-supervised by the chair of the department, Professor Dirk J. van Veldhuisen, MD, PhD.

Investigating Whether Epigenetic Reprogramming of Monocytes/Macrophages Contributes to the Development of Atherosclerosis

Niels P. Riksen, MD, PhD, internist and specialist in vascular medicine and head, Division of Vascular Medicine, Department of General Internal Medicine, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands, received a junior staff grant of €220,000 for the project titled “Trained Immunity as a Novel Mechanism in the Development of Atherosclerosis”. The research group of Mihai Netea, MD, PhD, professor of experimental internal medicine, from the same lab has demonstrated that not only the adaptive immune system, but also innate immune cells have an immunological memory: stimulation of monocytes/macrophages by various microorganisms induces a longlasting proinflammatory phenotype by epigenetic reprogramming. In a series of translational experiments, Dr Riksen and his team now aim to test the hypothesis that epigenetic reprogramming of monocytes/macrophages contributes to the development of atherosclerosis. Dr Riksen says, “The results of these studies will increase our understanding of the pathogenesis of atherosclerosis and may offer novel therapeutic targets to battle atherosclerosis.”

The research is conducted at the Lab of Experimental Internal Medicine and the Division of Vascular Medicine in collaboration with Professor Netea and Leo Joosten, PhD.

Analysing Admission Dynamic Contrast-Enhanced Computed Tomograms in Acute Ischaemic Stroke to Guide Treatment

Jan W. Dankbaar, MD, PhD, radiology resident, St. Antonius Hospital Nieuwegein, Nieuwegein, the Netherlands, and postdoctoral research fellow, University Medical Centre Utrecht, Utrecht, the Netherlands, received a physician in specialty training fellowship of ≈€150,000 for the project titled “Imaging Tissue Viability With Dynamic Contrast-Enhanced Computed Tomography in Acute Ischaemic Stroke Patients.” The award included a 3-year postdoctoral research fellowship (0.2 full-time equivalent) for himself and a 14-month postdoctoral research association (0.8 full-time equivalent) for Pieter C. Vos, MSc, PhD.

The aim of the project is to analyse admission dynamic contrast-enhanced computed tomograms in patients who have acute ischaemic stroke to determine reliable thresholds for defining the infarct core and to accurately discriminate hypoperfused tissue that is at risk of infarction from tissue that is adequately perfused by collateral arteries.

Dr Dankbaar says, “Our hypothesis is that if the part of the brain that is at risk of infarction is large compared to the infarct core the patient may benefit from recanalisation..."
Aiming to Identify the Signal Transduction Events Responsible for Hypertrophy Decompensation

Daan Westenbrink, MD, PhD, cardiology resident, Department of Cardiology, University Medical Centre Groningen, received a physician in specialty training fellowship of €150000 for the project titled “Role of A-Kinase Interacting Protein 1 in the Development of Heart Failure.” Myocardial hypertrophy is the evolutionarily conserved reaction to haemodynamic overload or injury intended to reduce ventricular wall stress. Although initially compensatory, reactive hypertrophy ultimately fails and progresses into a maladaptive cardiomyopathy with decreased survival. It would be therapeutically beneficial to retain the advantageous features of cardiac hypertrophy that reduce wall stress, while preventing its subsequent decompensation.

Dr Westenbrink says, “Our research aims to identify the signal transduction events responsible for hypertrophy decompensation, which may ultimately lead to novel therapies.” A-Kinase Interacting Protein 1 (AKIP1) is known to associate with the catalytic domain of protein kinase A, in effect blocking its function. Protein kinase A is a negative regulator of cardiac hypertrophy, so Dr Westenbrink and his colleagues propose that upregulation of AKIP1 during functional decompensation accelerates hypertrophy development.

The research project aims to define the role of AKIP1 in the hypertrophic response to distinct stimuli, and evaluate whether AKIP1 modulates hypertrophy development through inhibition of protein kinase A. Finally, the group will explore whether overexpression of AKIP1 affects heart failure development in vivo by generating AKIP1 transgenic mice.

The research will be primarily conducted at the University Medical Centre Groningen. Collaborators include researchers from the University of California San Diego, San Diego, CA: Erik Adler, MD, from the Department of Cardiology, Hemal H. Patel, PhD, from the Department of Anaesthesiology, and Professor Susan S. Taylor, PhD, from the Department of Chemistry and Biochemistry.

Investigating the Mechanisms Behind Accessory Pathway Formation

Rebecca Vicente-Steijn, PhD, junior postdoctoral fellow, Department of Anatomy and Embryology, Leiden University Medical Centre, Leiden, the Netherlands, was awarded a paediatric research fellowship of €150000 for a 2-year research project titled “Cardiac Development and Atrioventricular Re-entry Tachycardias: Mechanisms of Accessory Pathway Formation.” She says, “My research project focuses on the mechanisms of accessory pathway formation, the substrate responsible for atrioventricular reentry tachycardias, which represent 80% of the arrhythmogenic events in the fetus and the newborn.”

Clinical studies show that this patient population is heterogeneous (age of onset, type of substrate, and association with other congenital heart disease). The aim of the study is to provide new information on the pathogenesis and understanding of atrioventricular reentry tachycardias by studying the electrophysiology, anatomy, and molecular characterisation of accessory pathways in normal heart development and in a manipulated animal model. “The knowledge obtained in this study could result in new therapeutic strategies,” says Dr Vicente-Steijn.

Dr Vicente-Steijn will conduct the main part of her research between the Departments of Anatomy and Embryology (Monique R. M. Jongbloed, MD, PhD; Margot M. Bartelings, MD, PhD), Paediatric Cardiology (Professor Nico A. Blom, MD, PhD), Cardiology (Professor Martin Jan Schalij, MD, PhD; Daniel A. Pijnappels, PhD) and Molecular Cell Biology (Professor Marie-José Goumans, PhD).

“This fellowship also stimulates collaborations with foreign institutions for acquiring new skills and knowledge, thus improving the quality of my research,” says Dr Vicente-Steijn. “During the 2-year period I will travel to Prague in the Czech Republic to acquire expertise in optical mapping of embryonic hearts from the expert in this field, David Sedmera, PhD.”

Investigating the Pathological Changes in the Brain and Blood Vessels in Spontaneous Intracerebral Haemorrhage

C. J. M. (Karin) Klijn, MD, PhD, associate professor of neurology, University Medical Centre Utrecht, Brain Centre Rudolf Magnus, Utrecht, was awarded a clinical
ADAM17 are emerging as key regulators of various cell progression and stability. This remarkable activity implicates these enzymes in chemotactic factors, growth factors, and cytokine receptors. ADAM10 and ADAM17: Sheddases With Gate-Keeper and Immunomodulatory Functions Regulating Atherosclerotic Plaque Progression and Stability.

Dr Klijn says, “The results of these studies should enable the identification of the underlying vascular diseases in patients with spontaneous intracerebral haemorrhage beyond the so-far applied simplification of attributing deep intracerebral haemorrhage to hypertension and lobar intracerebral haemorrhage to cerebral amyloid angiopathy. My aim is to find ‘fingerprints’ of the vascular diseases that cause spontaneous intracerebral haemorrhage and find new entries for differentiated therapy for spontaneous intracerebral haemorrhage.”

The project is a collaboration between the University medical centres in Utrecht (Dr Klijn and neuroradiologist Jeroen Hendrikse, MD, PhD) and Leiden (neuroradiologist Professor Mark A. Van Buchem, MD, PhD, and neurologist Marieke J. H. Wermer, MD, PhD).

Investigating the Roles of ADAM10 and ADAM17 in Atherosclerosis

Marjo M. P. C. Donners, PhD, senior postdoctoral researcher, Cardiovascular Research Institute Maastricht received a junior postdoctoral fellowship of €250,000 for 4 years in 2007. This was followed in 2012 by a senior postdoctoral fellowship of €356,000, which includes a personal grant for a 2-year postdoc project and a 4-year PhD student project. Her project title is “ADAM10 and ADAM17: Sheddases With Gate-Keeper and Immunomodulatory Functions Regulating Atherosclerotic Plaque Progression and Stability”.

A disintegrin and metalloproteases ADAM10 and ADAM17 are emerging as key regulators of various cell functions by acting as molecular scissors, cleaving (shedding) cell surface molecules, such as adhesion molecules, chemotactic factors, growth factors, and cytokine receptors. This remarkable activity implicates these enzymes in various critical processes in atherosclerosis. Dr Donners says, “This project is an extension of my previous Dr E. Dekker fellowship, in which I identified ADAM10 as a novel mediator of vascular endothelial growth factor-induced endothelial cell functions regulating endothelial permeability and migration in angiogenesis.”

She adds, “I was the first to show ADAM10 expression in human atherosclerotic plaques associated with disease progression and angiogenesis.”

The current project aims to elucidate the roles and mechanisms of ADAM10 and ADAM17 in regulating atherosclerotic plaque progression and stability. The diagnostic and prognostic value of these enzymes will also be evaluated in patients who have cardiovascular disease. Dr Donners says, “This project will not only provide valuable information to develop novel therapeutic interventions, but may also provide novel diagnostic/prognostic tools.”

Major collaborators for this project are Professor Gerard Pasterkamp, MD, PhD, University Medical Centre, Utrecht (see http://circ.ahajournals.org/content/118/18/f103); Jaap van Buul, PhD, Sanquin Research, Amsterdam; Professor Dominique de Kleijn, PhD, National University of Singapore, Singapore; Professor Andreas Ludwig, PhD, Aachen University, Aachen, Germany; Professor Paul Saftig, PhD, Kiel University, Kiel, Germany; and Jacob Bentzon, MD, Aarhus University, Denmark.

Investigating the Role and Therapeutic Potential of Glucocorticoids in Low-High-Density Lipoprotein Cardiovascular Syndromes

Menno Hoekstra, PhD, postdoctoral research fellow, Division of Biopharmaceutics, Leiden Academic Centre for Drug Research, Leiden, was awarded a junior postdoctoral fellowship of €250,000 for 4 years in 2008 to conduct research on the relation between adrenal-derived steroid hormones and the development of cardiovascular disease. An adrenal transplantation technique in mice was introduced into the lab with the excellent technical help of Ronald J. van der Sluis, BSc. The work was done in collaboration with the clinical group of Jan Albert Kuivenhoven, PhD, and Professor Erik S. Stroes, MD, PhD, from the Amsterdam Medical Centre, and Professor Cheryl L. Wellington, PhD, from the University of British Columbia, Vancouver, Canada.

Dr Hoekstra says, “I have been able to reveal the importance of high-density lipoprotein-associated cholesterol as a substrate for the production of glucocorticoids by the
adrenals in mice and man.” In 2012, Dr Hoekstra was a awarded a 2-year funding extension and received a senior postdoctoral fellowship of €137000 for the project “The Role and Therapeutic Potential of Glucocorticoids in Low High-Density Lipoprotein Cardiovascular Syndromes.” He says, “Our aim is to validate the relevance of the steroidogenic function of high-density lipoprotein cholesterol for disease in the human general population and hopefully show whether steroid treatment is beneficial for subjects who exhibit genetically low high-density lipoprotein levels (hypoalphalipoproteinemia).”

Elucidating how Mast Cells Are Activated During the Development and Progression of Atherosclerosis

Ilze Bot, PhD, senior researcher, Division of Biopharmaceutics, Leiden Academic Centre for Drug Research, Leiden University, received a senior postdoctoral fellowship of €380000 for the project titled “Targeting the Mast(er) Cell: A Key Player in Cardiovascular Disease.”

Pathology studies have shown that mast cells accumulate in the atherosclerotic plaque during its progression, which may point to a direct causal role for mast cells in the process.

Dr Bot says, “We and others have previously demonstrated that perivascular mast cells contribute to atherosclerotic plaque destabilisation in mice. However, it is unknown how mast cells are activated during the disease process and by which mechanism they affect the progression of atherosclerosis and plaque destabilisation.”

Dr Bot and her colleagues hypothesise that mast cells are activated via atherosclerosis-specific pathways during disease progression, resulting in plaque destabilisation. Within this research programme, Dr Bot aims to elucidate how mast cells are activated during the development and progression of atherosclerosis, resulting in an enhanced incidence of acute cardiovascular events. Furthermore, she aims to explore potential therapeutic strategies to inhibit atherosclerotic lesion progression and prevent acute cardiovascular syndromes by modulation of mast cell function.

The research project will be carried out within the Division of Biopharmaceutics at the Leiden Academic Centre for Drug Research, which is headed by Professor Johan Kuiper, PhD. Dr Bot will work in collaboration with the Department of Surgery of Leiden University Medical Centre headed by Professor Paul Quax, PhD.

Elucidating the Mechanisms Underlying Adverse Cardiomyocyte Remodelling in the Failing Heart

Ralph J. van Oort, PhD, postdoctoral fellow, Department of Experimental Cardiology, Academic Medical Centre, Amsterdam, received a senior postdoctoral fellowship of €380000 for the project titled, “Aberrant mRNA Splicing Underlies Adverse Cardiac Remodelling in Heart Failure.”

Dr van Oort’s previous work focused on calcium signalling and transcriptional regulation in cardiac hypertrophy and heart failure. It is clear that a great variety of intracellular signalling pathways and transcription factors are able to initiate the cardiac hypertrophic response. In contrast, the signals that cause the progression of the initially adaptive hypertrophic response towards heart failure are largely unknown. End-stage heart failure is characterised by poorly contractile and dilated ventricles associated with lengthening of individual cardiomyocytes and loss of myofibrils. The mechanism underlying these adverse changes in cardiomyocyte structure remains to be elucidated.

Dr van Oort and his colleagues recently identified certain alternative splicing events in failing mouse hearts that potentially induce cardiomyocyte elongation and myofibril degeneration. The objective of this project is to characterise the extent and role of this alternative splicing in cardiomyocyte remodelling and heart failure. They will determine existing misbalances in alternative splice variants in both murine and human heart failure. They will also use different in vitro and in vivo approaches to assess the role of select splice variants in adverse cardiac remodelling. Dr van Oort says, “The long-term goal of this project is to elucidate the mechanisms underlying adverse cardiomyocyte remodelling in the failing heart, which could ultimately give rise to a new therapy for heart failure. Conventional clinical management of cardiac disease is aimed at underlying haemodynamic and neurohumoral changes. Our findings may lead to the actual structural remodelling process as a novel therapeutic target for cardiac disease.”

All experiments will be performed at the Department of Experimental Cardiology. Dr van Oort comments, “I am currently supervising 1 PhD student, and the Dr E. Dekker grant allows to me to hire an additional PhD student, who is expected to start this summer.”

Jennifer Taylor is a freelance medical journalist.