Funding: European Research Council Grants

Funding Pioneering Cardiovascular Research Projects in Europe

Recipients of European Research Council Advanced and Starting Grants describe the application process and the research funded by these grants to Jennifer Taylor, BSc, MSc, MPhil.

The European Research Council (ERC) provides substantial grants for cardiovascular disease research projects in the form of Advanced and Starting Grants.

**Advanced Grants**

ERC Advanced Grants up to €3.5 million (normally ≤€2.5 million) are awarded for up to 5 years to researchers with ≥10 years of experience who have established themselves as independent research leaders and leaders in their field. They support pioneering research projects in any field of science, engineering, and scholarship, and they encourage risk-taking and interdisciplinarity. Scientists of all nationalities are eligible, but the research must be conducted in a European Union (EU) member state or associated country. Applications should be submitted by a single principal investigator in conjunction with the host institution. They should include administrative forms, a research proposal, and supporting documentation, including a supporting statement from the host institution.

**Atheroprotect**

Christian Weber, MD, FESC, director of the Institute for Cardiovascular Prevention and chair in vascular medicine, Ludwig-Maximilians-University, Munich, Germany (see http://circ.ahajournals.org/content/119/24/f139.full.pdf+html), was awarded €2.5 million for 5 years by the ERC in 2009 for a structure–function analysis of the chemokine interactome for therapeutic targeting and imaging in atherosclerosis. The project is based on the newly introduced paradigm that heterodimer formation between chemokines constitutes a new regulatory principle amplifying specific chemokine activities while suppressing others, and thus shaping inflammatory cell recruitment and homoeostasis in atherosclerosis. Professor Weber and his team have established a map of the chemokine interactome, which provides the combinatorial diversity for functional plasticity and fine-tuning. The plan is to exploit this in an anti-inflammatory approach to selectively target vascular disease. So far, they have structurally determined heterodimers important in atherosclerosis using structure analysis and modelling to develop peptide-based therapeutic approaches specifically disrupting these heterodimers.

“...The application process was 2-tiered, and it took 2 to 3 weeks to prepare the annexes for both steps,” says Professor Weber. “...The completed evaluation of both rounds lasted ≈6 to 7 months before the final approval was conveyed in late 2009.” The project start was delayed to late 2010 when Professor Weber moved from RWTH Aachen University, Aachen, Germany, to Munich.

**TX-FACTORS**

Kari Alitalo, MD, PhD, research professor of the Finnish Academy of Sciences, Molecular/Cancer Biology Lab, Biomedicum Helsinki, University of Helsinki, Helsinki, Finland, was awarded €2.5 million for 5 years by the ERC in 2010 to investigate new biological functions and the therapeutic potential of vascular endothelial growth factors (VEGFs). The aim is to discover new disease-related...
functions and their signal transduction in cancer and cardiovascular disease and to establish preclinical models of effective therapy based on the molecular and biological biology of VEGFs, angiopoietins, angiogenesis, and lymphangiogenesis. The group will conduct studies based on their novel findings on the crosstalk between VEGF pathways in tumour angiogenesis, the involvement of lymphatic vessels in the development of obesity and associated inflammation, and the effects of VEGF-B on cardiac muscle and vessels. They will develop molecular, genetic, and induced pluripotent stem cell-derived models, and they will use functional genomics, proteomics, metabolomics, viral gene delivery, and blocking reagents from human antibody libraries.

The project was accepted in November 2010, but bureaucratic hurdles delayed its onset until June 2011. “The application process was in 2 stages: preliminary screen and final ranking,” says Professor Alitalo. “It was demanding but nowhere as laborious as the EU network grants that in my case (lymphangiogenomics) involved a collaborative effort of 13 labs. Overall, it is a great grant and this funding direction in the EU makes good sense to me.”

**ELABORATE**

Timothy John Aitman, FRCP, DPhil, FMedSci, professor of clinical and molecular genetics, MRC Clinical Sciences Centre, London, England, was awarded £2.48 million for 5 years by the ERC in 2011 to elucidate the molecular and functional basis of disease phenotypes in the rat model. His group previously sequenced the genome of the spontaneously hypertensive rat, which contains >750 genes that are completely or partly deleted or have a frameshift in their open reading frame, and is completing the Wistar Kyoto rat sequence. With ERC funding, Professor Aitman and his group will determine the functional consequences of genetic variants by creating and phenotyping transgenic and knockout rats on the spontaneously hypertensive and Wistar Kyoto rat genetic backgrounds. They will use transposon-mediated transgenesis and zinc-finger nuclease-mediated gene deletion. Genes will be prioritised for study by statistical and informatic analyses using their extensive physiological gene expression and linkage data in these rat strains, and by comparative analysis with data from human genome-wide association studies. Confirmed rat disease genes will be tested for conserved functions in humans.

Professor Aitman says, “These proposals provide a systematic route to elucidating the molecular and functional basis of disease phenotypes in spontaneously hypertensive and Wistar Kyoto rats, and for translating these findings to advance understanding of common human diseases.”

**ANGIOMIRS**

Stefanie Dimmeler, PhD, FESC, FAHA, professor of experimental medicine and director of the Institute of Cardiovascular Regeneration at the Centre for Molecular Medicine, Goethe University, Frankfurt, Germany, was awarded €2.38 million for 5 years by the ERC in March 2009 to investigate microRNAs (miRs) in vascular homeostasis, particularly in ischaemic diseases and aging. The funding has been used to hire 2 PhD students and 1 postdoc, purchase consumables, and generate 1 knockout mouse.

Professor Dimmeler and her colleagues have identified several miRs that exhibit crucial functions in endothelial cells. They have shown that the miR-17–92a cluster regulates the function of endothelial cells and that miR-92a can be targeted to augment neovascularisation after ischaemia. In further studies they identified several age-associated miRs, which may facilitate cardiovascular diseases in the elderly. Several miRs are dysregulated during aging, and some of these miRs impair vascular and cardiac function.

The study is “going smoothly,” says Professor Dimmeler. “Of course, it is a lot of work, in particular the study in aged animals, which is challenging.”

**FutureGenes**

Seppo Ylä-Herttuala, MD, PhD, FESC, professor of molecular medicine, A. I. Virtanen Institute and Department of Medicine, University of Eastern Finland, Kuopio, Finland, was awarded €2.5 million for 5 years by the ERC in early 2010 to investigate gene transfer techniques in the treatment of cardiovascular diseases and malignant glioma. It has enabled him to pursue a high-risk, innovative research project that will focus on the use of new VEGFs in the treatment of cardiovascular diseases. The project also involves vector development and brand-new aspects of small interfering and hairpin RNA technology that can be applied for the treatment of cardiovascular diseases.

“ERC Advanced Grants provide excellent opportunities for high-risk basic and translational research in virtually any area of biomedical research,” he says. “The ERC provides a flexible instrument for funding that can be used for hiring researchers and reagent and equipment purchases.” His group has used the funding to pay salaries to senior investigators and for reagent and animal costs. “The application process was straightforward, although because of the fierce competition, the research plan needs to be carefully described and justified,” adds Professor Ylä-Herttuala. After submitting the grant, the 2-step evaluation process took ~1 year before the final results were announced.

**MATHCARD**

Alfio Quarteroni, PhD, full professor in modelling and scientific computing, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, and Politecnico di Milano, Milan, Italy, was awarded €1.8 million for 5 years by the ERC in 2009 to carry out mathematical modelling and simulation of the cardiovascular system.

Professor Quarteroni is the founder and scientific director of the Lab for Modeling and Scientific Computing since...
2002 and of the Mathematics Institute for Computational Science and Engineering since 2009. MATHCARD is a collaboration between these 2 research institutions and is organised around 8 main topics covering mathematical models for the heart, perfusion, and the integrated cardiovascular system; numerical models allowing for control and optimisation; and software development, with special attention to clinical applications.

Less than one third of the project is financed directly by the EU. The team includes ≈15 senior scientists and 10 PhD students. “An important part of the preparation and execution of the project is the definition of the objectives and research topics,” says Professor Quarteroni. “This has required a clear vision on the whole lifespan of the project and then the coordination of many people carrying on their own research towards the achievement of challenging research results.”

EPIC-Heart
John Danesh, DPhil, FRCP, FFPH, professor of epidemiology and medicine and head, Department of Public Health and Primary Care, University of Cambridge, Cambridge, England, was awarded €2.5 million for 5 years by the ERC in May 2011 to investigate how diet, nutrients, and lifestyle factors modulate genetic susceptibility to coronary heart disease. The team has identified 12,000 people with coronary heart disease and 15,000 referents from a pan-European prospective study of diet and other lifestyle factors in 520,000 subjects. They will assay >217,000 genetic variants (in a metabolochip), 37 fatty acids, and vitamin D metabolites. Analyses will focus on the discovery of interactions, causal evaluation of biomarkers, and coronary heart disease risk scores. The findings should open new horizons and contribute towards explaining missing heritability, shaping nutritional guidelines, personalising preventive medicine, defining approaches to modify genetic susceptibility by avoiding deleterious lifestyles, and identifying biomarkers that are priority therapeutic targets and innovative prognostic tools.

“Gene–lifestyle interplay is a major future growth area,” says Professor Danesh. “This world-leading study will enhance Europe’s strengths in public health, nutrition, and genetic epidemiology and create a valuable future resource.”

Starting Grants
ERC Starting Grants are for researchers who have 2 to 12 years of experience after their PhD and are located in or moving to an EU member state or associated country. The research can be in any field of science, engineering, or scholarship. Applicants should have demonstrated their potential for research independence and in most cases will have produced at least 1 important article without their PhD supervisor. They should have a track record of early achievements, including significant main author articles and invited presentations. Submissions need to include administrative forms, a research proposal, and supporting documentation (supporting statement from the host institution and PhD certificate). Funding of ≤€2 million (normally ≤€1.5 million) is awarded for up to 5 years.

CHD-IPS
Karl-Ludwig Laugwitz, MD, professor of cardiology, Klinikum rechts der Isar and German Heart Center Munich, Technical University of Munich, Munich, Germany, was awarded a €1.8 million ERC Starting Grant for 5 years in March 2011 to model congenital heart disease in cardiovascular progenitors from patient-specific induced pluripotent stem cells. Professor Laugwitz’s research focuses on stem cell biology, cardiovascular development, and the characterisation of modelling mono- genetic and complex cardiac disease with human embryonic and induced pluripotent stem cells. The grant will be used for personnel (60%), consumables and mice (20%), and equipment (20%) to investigate the contribution of progenitor cells to cardiogenesis and the application of induced pluripotent stem cells to the modeling of cardiovascular disorders of genetic origin.

Professor Laugwitz says it took 1 month to think about the project and write the grant application. The interview process took place in Brussels, and from start to finish the evaluation took ≈9 months. “The ERC grant is a boost for my career and enables me to start a risky project that will have, if successful, a great impact in the field,” he says.

DYANIMIT
Daniel Razansky, PhD, head of the Experimental Biological Imaging Systems Lab and vice director of the Institute for Biological and Medical Imaging, Helmholtz Centre Munich and Technical University of Munich was awarded a €1.45 million ERC Starting Grant for 5 years in October 2010. Over the past 5 years, Dr Razansky has pioneered multispectral optoacoustic tomography, which can be used to follow the development of organs, cellular function, genetic expression, and disease progression in living tissues of small animals and potentially humans. His project aims to develop a novel high-performance optoacoustic imaging technology and explore its potential for neuroimaging and monitoring cardiovascular disease. Nearly 60% of the grant will be used to build a team of 3 postdoctoral researchers and 2 PhD students.

It took ≈3 months to write the grant. Dr Razansky says, “The final interview in Brussels was a bit stressful but professional and organised. The grant has definitely brought a broader European and international recognition on the highest level, increased the number of requests to give invited talks, and intensified media coverage. It also provided a solid and long-term ground for independent activities and building my own research group.”

Jennifer Taylor is a freelance medical journalist.
**Spotlight: Imre Janszky, MD, PhD**

Working on the Scandinavian Health Register “Goldmine” to Reveal Interesting and Important Cardiovascular Health Information

Imre Janszky, associate professor in epidemiology, Department of Public Health Sciences, Karolinska Institute, Stockholm, Sweden, and researcher in the Department of Public Health, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway, talks to Monika Polak, PhD.

By modifying insomnia symptoms, we might improve our cardiovascular health,” says Imre Janszky, MD, PhD, associate professor in epidemiology, Department of Public Health Sciences, Karolinska Institute, Stockholm, Sweden, and researcher in the Department of Public Health, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway.

Using Norwegian health survey data and following up 52,610 individuals over 11.4 years, Dr Janszky and his team recently demonstrated a dose-dependent association between the number of insomnia symptoms and the risk of acute myocardial infarction. Compared with people who never experienced sleep difficulties, the hazard ratios were 1.45 for difficulty initiating sleep almost every night, 1.30 for difficulty maintaining sleep almost every night, and 1.27 for a feeling of nonrestorative sleep more than once a week. Dr Janszky adds, “We had information on anxiety and depression symptoms and our analysis suggests that they act independently, so the problem with insomnia is not really explained.”

Although certain aspects of sleep and sleep problems such as sleep apnoea syndrome are known to affect cardiovascular and overall health, Dr Janszky says that sleep quality has not been investigated. He explains, “Some people can sleep for long enough but are not satisfied with their quality of sleep, so it’s a different question to sleep deprivation.”

Dr Janszky’s work on insomnia followed an investigation on the impact of Daylight Saving Time on the incidence of myocardial infarction. He explains, “The whole story started after the spring shift in 2008. I felt exceptionally bad after the change, and I checked the literature and no one had carried out any study on its effect on the heart.”

By investigating Swedish registry data on all acute myocardial infarctions in the country since 1987, Dr Janszky and his colleagues found a small but significant increase in the incidence of myocardial infarction after the transition to Daylight Saving Time in the spring, with women affected more than men. The researchers suggest that the results are due to the adverse effects of sleep deprivation on cardiovascular health, noting that other studies have shown sleep deprivation to be associated with a predominance of sympathetic activity and an increase in proinflammatory cytokines. Dr Janszky says, “Many people think it is just 1 hour that is lost in sleep, but it seems that for many individuals the sleep quality is also affected.”

“In Epidemiology We Believe in Big Numbers, and Cardiovascular Diseases Are Common, So We Can Feel Comfortable With Our Analysis”

Dr Janszky is Hungarian and was born in 1973. He followed his older brother, who is now a professor of neurology in Hungary, in pursuing a medical career and graduated with distinction from Semmelweis Medical University, Budapest, Hungary, in 1997. He then completed a PhD on the psychophysiology of panic disorder at the same institution in December 2000.

In 2000, Dr Janszky moved to the Karolinska Institute in Sweden, initially on a 6-month European Union grant to further his epidemiological and statistical knowledge. He says, “My Swedish colleagues then offered me a PhD position in epidemiology and public health. I moved into a research group interested in psychological factors and risk of myocardial infarction. In epidemiology we believe in big numbers and cardiovascular diseases are common, so it is a field where one can feel comfortable in one’s analysis.”

Dr Janszky completed his thesis on nonconventional risk and prognostic factors in coronary heart disease in 2005 under the supervision of Professor Staffan Ahnve, MD, PhD. His tutor at the Karolinska Institute was Anders Ahlbom, PhD, professor of epidemiology at the Institute of Environmental Medicine. Dr Janszky says, “His lectures were an eye-opener, and I had the privilege to work with him; he was a great influence on my own research and approach to problems.”

Approximately 90 percent of Dr Janszky’s time is spent on research, the rest on teaching epidemiology and statistics. He says, “I enjoy teaching statistics to medical doctors. The concepts are difficult, especially for people who do not have a strong mathematical background.”

Dr Janszky took up his research post at Trondheim in July 2010, and is now working with Professor Lars Vatten, MD, PhD. The time split between the Swedish and Norwegian institutions is fluid, with much of the Swedish work done via the Internet. His research in Norway centres on the Nord-Trondelag health study (HUNT) data, but he is involved in many projects, some solely in an analytical capacity.

In 2010, Dr Janszky published an article on the impact of stress, anxiety, and depression on cardiovascular health, specifically looking at early onset depression and anxiety and coronary heart disease risk. He believes the study is unique because it involved 49,321 Swedish men aged 18 to
among those undergoing both procedures.

“It Might Lead to Some Advance into How We Understand the Relationship Between the Immune System and Myocardial Infarction”

Involvement in cardiovascular disease research inevitably leads to a focus on inflammation at some point. Dr Janszky and his colleagues tackled this topic from the angle of tonsillectomy and appendectomy, proposing that if cardiovascular risk is altered for several immune-related disorders (eg, rheumatoid arthritis, inflammatory bowel disease), then undergoing procedures in childhood that involve removal of mucosa-associated lymphoid tissue, might also modify cardiovascular risk in later life. Their register-based study included data on 54 449 appendectomies and 27 284 tonsillectomies, with 5 randomly selected controls for each case, matched for sex, age, and country of residence. People undergoing these procedures before age 20 were found to have an increased risk of acute myocardial infarction, with adjusted hazard ratios of 1.33 for appendectomy and 1.44 for tonsillectomy; the highest risk was among those undergoing both procedures.

The results are consistent with the hypothesis that subtle alterations in immune functions after these procedures may alter subsequent cardiovascular risk. Dr Janszky says, “It might lead to some advance into how we understand the relationship between the immune system and myocardial infarction.” One of Dr Janszky’s coauthors on this article was Kenneth Mukamal, MD, MPH, associate professor at Harvard Medical School and the Beth Israel Deaconess Medical Centre, Boston, MA. Dr Janszky says, “Dr Mukamal was extremely helpful, and I learned a lot from him. I hope we will work together for a long time.”

Dr Janszky adds that he was pleased to receive a “nice mail” about this study from Göran Hansson, MD, PhD, professor of experimental cardiovascular research at the Karolinska Institute, 1 of the first researchers to come up with the idea that atherosclerosis is an inflammatory disease (see http://circ.ahajournals.org/content/124/14/1979.full.pdf+html).

Statistics has played an “essential” role in Dr Janszky’s research career. He says, “Usually medical doctors are not experts in statistics. However, statisticians often do not understand medical problems, so it has always been appreciated by colleagues and bosses that I had expertise in both fields.” Recently, Dr Janszky has been investigating a novel approach to quantifying random error in epidemiological studies. He explains, “Many statisticians and epidemiologists strongly believe that the concept of statistical significance should be abandoned. We proposed a method that each study can be compared to a theoretical gold standard study in terms of precision. We feel that this could lead to a better understanding of the amount of random error behind each result in a typical study.”

In the future, Dr Janszky plans to continue working with the Scandinavian health register “goldmine.” “There are so many data, and they provide interesting and important messages, so I plan to use them even more, especially now that I am in both Sweden and Norway,” he says. “Scandinavia is not only a dreamland for epidemiologists, but also for mushroom lovers,” adds Dr Janszky, who learned to identify mushrooms from his father, a physicist, who passed a state exam on mushroom identification. Dr Janszky and his Hungarian wife and 2-year-old daughter now live in Norway, but Dr Janszky maintains regular contact with his native Hungary and still works with Professor Maria Kopp, MD, PhD, director of the Institute of Behavioural Sciences at Semmelweis Medical University, who encouraged him to study epidemiology and statistics.

References

Headshot photo courtesy of Hanne Strypet.

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European Meetings Update

18 January to 29 February, 2012

18 to 21 January
Ninth Gulf Heart Association Conference
Muscat, Oman
For further details, contact:
heart.oman@gmail.com

20 to 20 January
EHRA Webinar - Mechanisms of Arrhythmia and its Clinical Implications
For further details, see:

29 to 31 January
ESC Global Scientific Activities at the 23rd Annual Conference of the Saudi Heart Association
Riyadh, Saudi Arabia

29 to 31 January
Integrated Management of Acute and Chronic Coronary Artery Disease
Innsbruck, Austria
For further details, contact:
csconcept@chello.at

31 to 31 January
ESC Webinar on Clinical Management of Treatment Resistant Hypertension
For further details, see:

2 to 3 February
31st Annual Scientific Meeting of the Belgian Society of Cardiology
Brussels, Belgium
For further details, contact:
secretariat@bvc-sbc.be

9 to 9 February
4th British Society for Heart Failure Medical Training Meeting
London, England
For further details, contact:
info@bsh.org.uk

10 to 10 February
Heart Failure Nurse Study Day
London, England
For further details, contact:
info@bsh.org.uk

15 to 15 February
Arrhythmia Highlights at the ESC 2011 Meeting: Relevance for General Cardiologists in Daily Practice
For further details, see:

21 to 21 February
ESC Webinar on Acute Coronary Syndrome for the Rest of Us
For further details, see:

23 to 25 February
Advanced Invasive Cardiac Electrophysiology
Sophia Antipolis, France
For further details, see:

26 to 29 February
ESC Webinar on Peripheral Arterial Disease: A Clinical Case Based Approach
For further details, see:

29 February to 3 March
Winter ISHNE 2012
Zakopane, Poland
For further details, see:
http://www.winterishne2012.senit.pl/

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