The Spanish Society of Cardiology offers a number of grants for cardiologists to carry out basic, clinical, translational, and epidemiological research. Vicente Bodi, MD, PhD, FESC, FACC, full professor of medicine, Department of Medicine, School of Medicine and Dentistry, University of Valencia; head of the Group on Translational Research in Ischemic Heart Disease, Medical Research Foundation INCLIVA, Valencia; and cardiologist, Cardiology Department, Hospital Clinico Universitario, Valencia, Spain

Professor Bodi has received 4 research grants as principal investigator from the Spanish Society of Cardiology over the past 8 years. The projects have investigated the evolution of left ventricular volumes and systolic function after acute myocardial infarction and the role of the coronary microcirculation (funded in 2004), the prognostic value of vasodilator stress perfusion cardiac magnetic resonance in patients with known or suspected ischaemic heart disease (2007), acute deregulation of the immune system in acute myocardial infarction and assessment of experimental therapeutic options (2008), and the efficacy of local gene therapy for reducing infarct size and microvascular obstruction in a swine model of myocardial infarction (2009).

The 2004 and 2007 grants were used in the design and management of databases and development of a core lab on cardiac imaging, enabling a line of research on the pathophysiology and risk stratification of ischaemic heart disease using cardiac magnetic resonance. This allowed Professor Bodi’s group to undertake 2 large prospective cardiac magnetic resonance registries including >3000 patients with ST-segment elevation myocardial infarction (STEMI) and stable ischaemic heart disease. They comprehensively assessed the structural consequences of infarction on the left ventricle in STEMI to accurately predict late systolic recovery and to improve risk stratification.

In patients with stable ischaemic heart disease, the group validated the utility of stress cardiac magnetic resonance in the risk stratification and the decision-making process.

The 2008 and 2009 grants have provided the seed for a move into translational research. The group’s clinical studies are coordinated from the Cardiology Department of INCLIVA, in cooperation with Spanish hospitals and cardiovascular networks. Their basic science studies involve an intense multidisciplinary cooperation with groups from the Valencia University Campus of Excellence. There is also a fruitful cooperation with the University of Regensburg, Regensburg, Germany. Experimental models of ischaemia and infarction have been developed, and in this way, they have moved towards a translational view of ischaemic heart disease in different fields, such as the role of the immune system in the pathophysiology of myocardial infarction. They recently published a metabolomic biosignature of acute myocardial ischaemia that, in the future, with further validation, could be helpful for a biochemical diagnosis of unstable angina in emergency departments.

Professor Bodi says, “On the basis of our experience in clinical and basic research, our intention now is to advance...”
further in the understanding of the role of the immune and metabolic systems on the pathophysiology of STEMI and subsequently explore new complementary therapeutic options.”

Before receiving funding from the Spanish Society of Cardiology, some of Professor Bodi’s most relevant previous contributions included the creation of simple clinical and multimarker scores that accurately predict risk of events in patients with non ST-segment elevation acute coronary syndromes, and an investigation of myocardial viability and ventricular remodelling in STEMI patients.

Professor Bodi comments, “The funding from the Spanish Society of Cardiology has fuelled us, not only in terms of personnel and equipment, but also in motivation, thus laying the foundation for our group on translational research. Second, the grants resulted in an encouraging recognition from the Spanish Society of Cardiology, such as the awards for the best articles published in Revista Española de Cardiología in 2005 and 2010.” He adds, “And last but not least, these projects have resulted in a meticulous follow-up of our patients, which, undoubtedly, has resulted in better care.”

References

David Garcia-Dorado, MD, PhD, FESC, FACC, head, Lab of Experimental Cardiology and Cardiovascular Research Program, Hospital Universitari Vall d’Hebron–Institut de Recerca, Universitat Autònoma de Barcelona, Barcelona, Spain

Professor Garcia-Dorado has, along with other members of his group, made many successful applications to the Spanish Society of Cardiology for small project grants. “We have won many, probably >12, in the past 10 years,” he says. “These grants, although quite small (€12000 to €18000 for 2 years) have been useful for our group. They have complemented funding for expensive projects, and quite often they have allowed us to start a project or test an idea before getting an official grant. This process has proved extremely useful because it has helped us be more competitive in our grant applications by allowing us to refine new proposed hypotheses and methodologies.”
In addition, the grants are flexible, and they have been used in some instances to cover expenses not initially considered in a public-funded project. Professor Garcia-Dorado and his group have taken advantage of these grants for lab investigation studies (eg, to perform initial studies to interfere with postinfarction remodelling through miRNA inhibition), clinical research (eg, to investigate the mitochondrial genes in heart failure and the determinants of evolution of aortic aneurysm), and epidemiological and outcome research studies (eg, for transcatheter aortic valve implantation).

Professor Garcia-Dorado says, “These grants have been invaluable in stimulating the first steps of many young cardiologists and nonmedical graduates in cardiovascular research.”

Professor Crespo-Leiro says, “This photo shows the senior investigators in our group. I am the one with the blue tie, in the front row.” Photograph courtesy of Professor Garcia-Dorado.

Marisa G. Crespo-Leiro, MD, PhD, FESC, head, Advanced Heart Failure and Heart Transplantation Unit, Cardiology Service, Hospital Universitario A Coruña, La Coruña, Spain

Professor Crespo-Leiro received a grant from the Spanish Society of Cardiology in 2011 to study the potential use of indoleamine 2,3-dioxygenase as an early serum marker of allograft rejection after heart transplantation. This funding is contributing to basic and translational research by a multidisciplinary team that includes university hospital specialists in heart failure and heart transplantation, biologists and basic researchers at the Biomedical Research Institute A Coruña, and an epidemiologist at the Instituto de Ciencias de la Salud of the University of A Coruña.

Since its formation in 1993, Professor Crespo-Leiro’s group has cared for >640 heart transplantation patients and has investigated many clinical aspects of heart transplantation, including risk factors, noninvasive diagnosis of rejection, antibody-mediated rejection, and post-heart transplantation complications (eg, cytomegalovirus infection, renal dysfunction, neoplasias, etc.). Some of this work has consisted of analyses of data recorded in the Spanish Post-Heart Transplant Tumour Registry, which is coordinated by Professor Crespo-Leiro. This online registry collects data on all post-heart transplantation neoplasias in Spain and has provided information on the incidence of, risk factors for, and survival after post-heart transplantation neoplasias.

Particularly useful information has been obtained concerning lung and skin cancers, as well as the influence of antiviral prophylaxis and induction therapy on the development of lymphomas.

Professor Crespo-Leiro’s group has also taken part in international drug trials and multicentre studies, such as the second Cardiac Allograft Rejection Gene Expression Observational Study, which aims to evaluate whether the expression levels of certain genes in peripheral blood monocytes allow noninvasive diagnosis of allograft rejection after heart transplantation.

Indoleamine 2,3-dioxygenase is an enzyme that initiates the catabolisation of tryptophan via kynurenines. It is inducible in several cell types, including monocytes,
macrophages, and dendritic cells. It assists the immune response by denying tryptophan to pathogens in the proximity of the cells that produce it, and it also has immunosuppressive effects, mainly on T-helper 1 cells. It is induced by cytokines, mainly interferon gamma, and by the binding of cytotoxic T-lymphocyte-associated antigen 4, whether presented on a T cell surface or in solution as cytotoxic T-lymphocyte-associated antigen 4-Ig, and it seems to form part of a negative feedback loop that regulates T cell proliferation. Thus, T cell proliferation after organ transplantation is accompanied by upregulation of indoleamine 2,3-dioxygenase in appropriate cells, and this increase in indoleamine 2,3-dioxygenase is detectable in peripheral blood samples through its effects on serum levels of tryptophan and kynurenine.

Patients with transplanted kidneys have higher kynurenine/tryptophan ratios than healthy controls, and on average, patients who suffer acute rejection during the first 3 weeks after transplantation have higher kynurenine/tryptophan ratios during this period than those who do not. Furthermore, this difference between rejectors and nonrejectors appears earlier than differences in serum creatinine, holding out the possibility of noninvasive early detection of rejection.

To determine whether similar alterations in the serum kynurenine/tryptophan ratio herald the rejection of transplanted hearts, Professor Crespo-Leiro’s group determined this ratio in 98 heart transplantation patients 1 month after transplantation and recorded episodes of acute cellular rejection during the next 11 months. She says, “The results were presented at the 32nd annual meeting of the International Society of Heart and Lung Transplantation and at the 2nd meeting of the Spanish Transplantation Society. We hope that the results obtained with the financial support of the Spanish Society of Cardiology will lead to reliable noninvasive identification of prerejection status, allowing immunosuppressive therapy to be tailored to the particular risk of the individual patient.”

References


**Antonio Berruezo, MD, PhD, senior specialist, Arrhythmia Section, Thorax Institute, Hospital Clinic, University of Barcelona, Barcelona**

Dr Berruezo received a clinical research scholarship from the Spanish Society of Cardiology in 2008 to support an investigation of ventricular arrhythmias. He says, “This scholarship allowed me to start a line of research on the analysis of the substrate related to ventricular arrhythmias and to investigate the usefulness of high-resolution, contrast-enhanced cardiac magnetic resonance to guide ventricular tachycardia ablation procedures.”

Dr Berruezo has been using the funding, along with additional resources from the Instituto de Salud Carlos III of the Health Ministry of the Spanish Government, the European Heart Rhythm Association Training Fellowship Programme, and Siemens Healthcare, to obtain materials and equipment and to support a team of research electrophysiology fellows and engineers devoted to this investigation line. All of the team have contributed to progress in this research line, with original work published in high-impact factor journals, including 2 recent articles in *Circulation: Arrhythmia and Electrophysiology.*

Dr Berruezo says, “During this time, I have also been working with Professor Lluís Mont, MD, PhD, and Professor Josep Brugada, MD, PhD, sharing with them decisions on work plans and receiving their invaluable inputs, and a good relationship has been established with the cardiac imaging team (Jose Ortiz-Pérez, MD, PhD, Teresa de Caralt, MD, PhD, Rosario Jesús Perea, MD, PhD, and Marta Sitges, MD, PhD) based on mutual confidence and commitment to the project.”

Dr Berruezo and his colleagues are studying the ventricular fibrotic tissue scar, which is the substrate for ventricular arrhythmias. They are analysing the significance of its presence, its relationship with different biomarkers of the extracellular matrix turnover, and the predictive value of its identification and characterisation with respect to the cardiovascular outcomes. They have found that the presence, size, and heterogeneity of myocardial scar independently predicts appropriate intracardiac device therapy in cardiac resynchronisation therapy candidates and that contrast-enhanced cardiac magnetic resonance-based scar analysis might help identify a subgroup of patients at relatively low risk of sudden cardiac death. The team is also investigating the usefulness of pre- and postprocedural cardiac imaging for the planning, guidance, and evaluation of ventricular tachycardia ablation procedures. For this purpose, they have developed postprocessing software in close collaboration with engineers from the Department of Information and Communication Technologies, Pompeu Fabra University, Barcelona.

Dr Berruezo says, “We have found that scar characterisation by means of high-resolution contrast-enhanced cardiac magnetic resonance resembles that of electroanatomical voltage maps and can be integrated into the navigation system to guide and facilitate the ventricular tachycardia ablation.”
Dr Berruezo has been carrying out research on ventricular arrhythmias since 2003 and has also participated in other research areas, including cardiac resynchronisation therapy and atrial fibrillation ablation (also partially funded by scholarships from the Spanish Society of Cardiology).

“The scholarship from the Spanish Society of Cardiology has played an important role because it permitted me to start with this investigation line in 2008,” says Dr Berruezo.

“Although the funding was not enough to maintain a growing and productive research team and to acquire the necessary materials and equipment, it was the beginning of an exciting avenue of research.”

References

Jennifer Taylor is a freelance medical journalist.

Funding: L’Oréal–United Nations Educational, Scientific, and Cultural Organisation for Women in Science Awards

Elza D. van Deel, PhD, postdoctoral researcher, Department of Cell Biology and Genetics, Erasmus Medical Center, Rotterdam, the Netherlands, and Department of Cardiovascular Science, National Heart and Lung Institute, Imperial College London, London, England, received a L’Oréal–United Nations Educational, Scientific, and Cultural Organisation for Women in Science award in 2012. She describes the award and her research to Jennifer Taylor, BSc, MSc, MPhil.

Elza D. van Deel, PhD, postdoctoral researcher in the Department of Cell Biology and Genetics at the Erasmus Medical Center, Rotterdam, the Netherlands, received a L’Oréal–United Nations Educational, Scientific, and Cultural Organisation (UNESCO) for Women in Science award in 2012 to carry out cardiovascular stem cell research in the Department of Cardiovascular Science, National Heart and Lung Institute, Imperial College London, London, England (see http://circ.ahajournals.org/content/125/24/f139) under the supervision of Professor Michael D. Schneider, MD, FMedSci (see http://circ.ahajournals.org/content/125/16/f91). The For Women in Science partnership between L’Oréal and UNESCO was formed in 1998. Each year they give out a number of awards. Since 2000, this funding has included 15 international fellowships each year for promising women working in the life sciences at the doctoral or postdoctoral level. Three international fellows from each of the 5 UNESCO regions (Africa, Arab States, Asia/Pacific, Latin America/Caribbean, and North America/Europe) are chosen to continue their research in prestigious institutions outside their home country. Each fellowship provides maximum funding of $40,000 and may cover a period of up to 2 years. The 15 UNESCO–L’Oréal international fellows...
for 2012 were chosen for the excellence and feasibility of their proposed projects and for the potential impact of their research on people’s lives or on the environment.

Dr van Deel received $20000 for her first year of research and has the possibility of extending the fellowship with an additional $20000 for the second year. She will investigate the influence of the extracellular matrix protein fibulin-4 on the development of cardiomyocytes and cardiac pathology. She hopes to demonstrate that fibulin-4 influences the molecular signals necessary for stem cells differentiating into cardiomyocytes and that lack of fibulin-4 results in abnormalities in cardiac development that increase cardiac vulnerability to pathological stimuli. She says, “This will bring new insight into the cardiac dysfunction and hypertrophy observed in connective tissue diseases like Marfan syndrome and cutis laxa syndrome and, consequently, give rise to new approaches for treating cardiovascular abnormalities in these patients.”

Additionally, because fibulin-4 is a critical component for the structural integrity and elasticity in many organs besides the heart, the development of an in vitro cell model of reduced fibulin-4 expression will also create new scientific tools for the translational research of diseases such as aortic aneurysm or accelerated skin ageing, which are similarly induced by distortions in connective tissue assembly.

During her PhD project, Dr van Deel investigated how several factors such as exercise, oxidative stress, nitric oxide, and ageing affect the development of left ventricular remodelling and dysfunction after severe pressure overload and myocardial infarction using transgenic mouse models. She did most of the research with Professor Dirk J. Duncker, MD, PhD, and Professor Jan H. J. Hoeijmakers, PhD, in the Department of Cardiology, Erasmus Medical Center. Part of the work was carried out with Yingjie Chen, MD, PhD, and Robert J. Bache, MD, at the Center for Vascular Biology, Department of Medicine, University of Minnesota Medical School, Minneapolis, MN. Dr van Deel demonstrated that the beneficial effects of exercise training on cardiac remodelling and dysfunction are critically dependent on the underlying pathogenesis.1 She also established the protective role of extracellular superoxide dismutase after myocardial infarction2 and showed that the beneficial effects of endothelial nitric oxide synthase, which are observed after myocardial infarction, are lost in the pressure overloaded heart because of endothelial nitric oxide synthase-induced oxidative stress.3

“Before receiving this grant, my research was predominantly focused on cardiac physiology,” says Dr van Deel. “With this award, I can enter a new field of research that is more oriented towards molecular cell biology. Consequently, in my future career, I will be able to combine diverse molecular in vitro and in vivo disciplines offering great scientific synergy. The grant provides excellent opportunities to develop myself as a scientist and opens interesting doors for the future.”

Jennifer Taylor is a freelance medical journalist.

References
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