

Current State of Basic and Translational Cardiovascular Research in Spain

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Although the risk of developing cardiovascular disease (CVD) is reduced by the Mediterranean diet,¹ CVD prevalence in Spain is rising. CVD is a major cause of mortality and morbidity in this country, and there is a growing awareness in the scientific community of the need for advances in knowledge, diagnosis, and therapy.

Spain has a strong tradition of basic research in molecular biology, immunology, development, neuroscience, and oncology, but historically there have been few research groups dedicated to basic cardiovascular research, and this has been reflected in limited funding. Over the last 20 years, a national strategy to address this situation has seen the creation of a cardiovascular center of excellence and research networks focused on CVD. This significant boost to Spanish cardiovascular research has generated closer collaboration between the clinical and basic research communities, with already tangible beneficial results for patients. Here, we outline current trends in cardiovascular research in Spain, highlighting achievements, opportunities, and challenges.

Cardiovascular Research in Spain: Facts and Figures

Grants and Funding

Despite increasing CVD incidence and prevalence, public research funding in Spain has decreased over the last decade. This cut in funds follows a general trend in Spain in the wake of the global financial crisis. In 2016, the Ministry of Economy and Competitiveness, which is the main public funding body in Spain, spent around 380 million euros on different project grants, mainly in the so-called Excellence, Societal Challenges, and Health Research Projects programs. The Excellence call funded >700 grants (42% success rate), averaging around 100 000 euros per project. The Societal Challenges awarded 1500 grants (49% success rate) with 145 000 euros each on average. The Health Research Projects scheme funded >600 projects with an average of 95 000 euros each (36% success rate). These projects are 3 to 4 years long and were awarded to 1, or sometimes 2, principal investigators. Over the last 8 years, basic and

translational cardiovascular research groups have obtained around 300 competitive grants, securing close to 50 million euros (Figure [A]).

Over the last 15 years, the *Instituto de Salud Carlos III* (ISCIII; Carlos III National Institute of Health) has provided an additional funding stream to support thematic research networks. These networks are multidisciplinary and bring together basic and clinical researchers in an effort to elucidate new disease mechanisms and develop new diagnostic and therapeutic tools that will ultimately improve health-care. The CVD dedicated network (CIBER de Enfermedades Cardiovasculares [CIBERCV]) is discussed below in more detail. Another source of funding for CVD studies and training is the *Sociedad Española de Cardiología* (SEC; Spanish Society of Cardiology). Grants from the SEC are small ($\leq 25\,000$ euros per project), but the SEC funds a large number of projects every year, amounting >800 000 euros through different grant and fellowship programs.

Spanish cardiovascular research groups also receive significant support from international sources, with 50 groups awarded competitive international grants amounting >26 million euros over the last 5 years (Figure [B]). These are mainly European Union grants awarded to networks of researchers working toward a shared goal. Some of these networks focus more on research training (Innovative Training Networks), while others are fully focused on research. Although the number of European grants with participating Spanish groups is increasing and approaching that of other countries with a stronger tradition in cardiovascular research, there is still room for improvement. European grant calls (especially within the current Horizon 2020 program) have taken on a more clinical and applied slant, forcing closer interactions between basic and clinical researchers. The transition to more applied collaborative research is already underway in Spain, thanks to the initiatives mentioned above, and this established trend should, therefore, increase Spanish participation in continental networks. In addition, several selected researchers have received funding from the European Research Council in the form of individual grants. These prestigious grants are competitive

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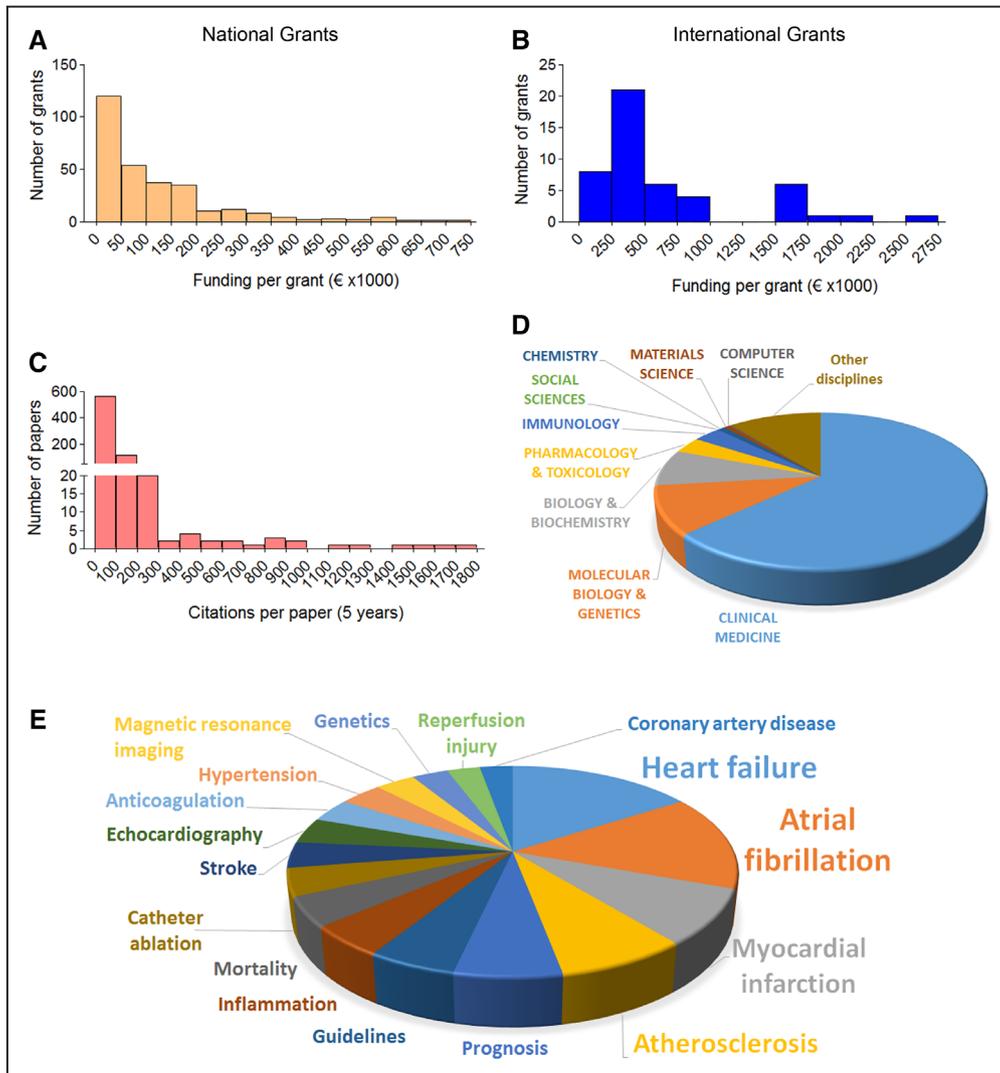


Figure. Active grants and publications in Spanish cardiovascular research, 2012 to 2016. **A** and **B**, Distribution of national (**A**) and international (**B**) grants awarded to Spanish cardiovascular research groups. For network grants, the funding share corresponding to each Spanish group was calculated. **C**, Distribution of citations received by publications by Spanish groups involved in cardiovascular research. **D**, Distribution of journal categories for articles published by Spanish cardiovascular research groups. **E**, Keyword distribution in papers published by Spanish cardiovascular research groups.

(10% success rate) and generously funded (1.5–3 million euros for a 5-year project). A few groups have also been awarded grants from American and transatlantic institutions, amounting 2.3 million euros overall.

Publications

Despite the historical difficulties outlined earlier, Spanish cardiovascular research groups have a strong record in high-impact publication, with >2500 papers published in the last 5 years. Of these, 68% were published in journals with an impact factor in the first quartile, and 29% of the publications were in the first decile. These figures are higher than the average impact of Spanish papers published in the medical sciences, of which 48% were published in Q1 journals. Moreover, the normalized citation impact for Spanish cardiovascular research papers (the number of citations for these papers divided by the average number of citations for all papers in the same period and field) was 2.9 in 2014, compared with 1.4 for all Spanish

medical science papers in the same period. Consistent with these indicators, 29% of the 2500 Spanish cardiovascular research papers published in the last 5 years were among the top 10% cited papers in their area and >100 were among the top 1%. The citation distribution per paper is shown in Figure (C).

Almost two thirds of these articles were published in clinical journals, followed by journals specialized in molecular biology and genetics, biochemistry, pharmacology, and immunology (Figure [D]). A keywords analysis for each paper showed enrichment for major cardiovascular conditions, including heart failure, atrial fibrillation, myocardial infarction and stroke, atherosclerosis, and terms related to prognosis and treatment, imaging, and major CVD symptoms (Figure [E]).

Together, these data show that cardiovascular research in Spain is in good health, despite the funding restraints, with strength in clinical and translational cardiology, as well as in molecular biology, genetics, and immunology. Three representative examples of Spanish accomplishments are (1) the study

of the benefits of the Mediterranean diet in the PREDIMED (Primary Prevention of Cardiovascular Disease With a Mediterranean Diet) randomized clinical trial,¹ showing a reduction in major cardiovascular events in high-risk subjects allocated to a Mediterranean diet supplemented with extravirgin olive oil or nuts. (2) The translational study of the cardioprotective effect of metoprolol when administered early in the course of a myocardial infarction.² This translational program included the METOCARD-CNIC (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction) randomized clinical trial, showing a reduction in infarct size and microvascular obstruction, along with an increase in long-term left ventricular ejection, in myocardial infarction patients receiving intravenous metoprolol before reperfusion, and a mechanistic study unraveling the mechanism by which metoprolol protects the heart from ischemia/reperfusion injury (ie, by targeting neutrophils). (3) The development of the secondary prevention *Fuster-CNIC-Ferrer* cardiovascular polypill, which includes aspirin, an angiotensin-converting enzyme inhibitor, and a statin.³ This program includes the execution of the FOCUS (Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention) randomized clinical trial, showing that postmyocardial infarction patients allocated to a polypill strategy show a significantly higher adherence to medication, and the ongoing SECURE (Secondary prevention of cardiovascular disease in the elderly trial) clinical trial, examining whether the polypill strategy reduces major cardiovascular events in postmyocardial infarction patients.

Challenges and Opportunities

Personalized Medicine and Big Data

Spain has a world-class public healthcare system, and the integration of different hospital databases into larger regional and national resources opens up new possibilities for the analysis of big data and the development of personalized medicine. In this regard, new projects characterizing participants at the clinical, behavioral, and molecular level have emerged. A prime example is the PESA study (Progression of Early Subclinical Atherosclerosis),⁴ led by the Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC; see below). This middle-aged CVD-free cohort study is a unique initiative in Spanish research focused on primary prevention, not only in terms of cohort size (n=4000) but also because of the deep patient phenotyping, including advanced noninvasive techniques and the original funding scheme.⁵ The long-term CVD-dedicated PESA study is funded by an innovative public-private partnership in which the public funds come from the ISCIII (through the CNIC) and the private funding from Banco Santander.

Genetics

Traditionally, as in other areas of the Mediterranean basin, Spanish citizens have tended to live close to their families and place of birth. From a scientific perspective, this translates into large pedigrees that considerably facilitate genetic studies. Patients and their families are generally keen to cooperate with such studies and represent a major resource for the identification of CVD-associated mutations. In addition, patients are usually well phenotyped, and clinicians are willing

to share valuable samples to improve genetic studies. These features of the Spanish cultural landscape have been exploited for the study of several diseases, including dilated, hypertrophic, and arrhythmogenic right ventricular cardiomyopathies and familial hypercholesterolemia.⁶⁻⁸

Medical Engineering and Imaging

In recent years, a strong bond has emerged between biomedicine, engineering, and physics, extending to the creation of new university departments and degrees. This partnership has contributed to the development of new research and diagnostic imaging tools, including both hardware and software. In addition, joint efforts by engineers and cardiovascular researchers have facilitated the development of image post-processing methods that have improved the accuracy of diagnostic imaging.

Regenerative Medicine

At the beginning of the 2000s, Spanish researchers enthusiastically embraced the various initiatives in regenerative medicine, particularly in relation to regenerative cardiology. This discipline bloomed with the creation of new departments in major research institutes, international meetings held in Spain, and government financial support. Although the financial crisis slowed the pace of research somewhat, several research groups maintain active research programs on regenerative medicine in the cardiovascular field. Spanish groups led a recent position paper by the Transnational Alliance for Regenerative Therapies in Cardiovascular Syndromes (TACTICS),⁹ which was created with the goal of improving clinical applications in cardiovascular regenerative medicine. This document will pave the way for future translational regenerative research and illustrates Spanish leadership in collaborative approaches to translational regenerative medicine.

New Paradigms in Translational Cardiovascular Research in Spain

To bridge the divide between basic and clinical research, the Spanish government launched 2 initiatives >10 years ago: the CNIC, a research center of excellence focused on translational cardiovascular research, and the CIBERCV, a virtual center that integrates 40+ basic and clinical groups into a national research network.

CNIC

The CNIC is a modern research institute founded in 1999 by the Spanish Ministry of Health to tackle the CVD epidemic.¹⁰ Covering a total floor space of 23 000 m², the center was equipped from the outset with the latest scientific equipment and technical units and has built a powerful, cross-disciplinary research base that embraces basic research, as well as population and clinical studies. Under the umbrella of 2 interconnected departments, Basic Research and Clinical Research, the 29 research groups at the CNIC are strategically distributed into 3 research areas: (1) Vascular Pathophysiology (research programs: vascular biology; signaling and inflammation), (2) Myocardial Pathophysiology (research programs:

myocardial biology; cardiovascular metabolism), and (3) Cell and Developmental Biology (research programs: genetics and development; cell biology and physiology). Each of the research areas includes basic and clinical researchers. Under the leadership of Dr. V. Fuster since 2005, the CNIC is financed through an innovative public-private financing structure that includes direct governmental funding through the ISCIII and private sector through the Pro CNIC Foundation (a diverse consortium of 14 leading Spanish companies and charitable foundations; <https://www.fundacionprocnic.es/miembros.php>). The CNIC has also achieved major success in securing competitive funding, with CNIC groups coordinating several European FP7 and H2020 projects and securing 10 European Research Council individual grants in the last few years. The center's performance is monitored by an external Scientific Advisory Board, which makes recommendations about the recruitment of new group leaders and evaluates all of the CNIC's scientific activities and the performance of its group leaders according to an up-or-out system.

The CNIC is establishing strong bonds with hospitals across Spain (and internationally) to promote closer integration between basic and clinical research. To boost these interactions, between 2008 and 2013, the CNIC funded collaborative translational research projects (only 25% of them led by CNIC researchers) with a total of 6.4 million euros ($\approx 800\,000$ euros per project). Landmark clinical trials arising from this highly successful CNIC-translational initiative included the PREDIMED¹ and METOCARD-CNIC trials.² CNIC also coordinates European initiatives that include the participation of many Spanish clinical centers, for example, the SECURE and FOCUS trials³ within the polypill initiative led by CNIC General Director Valentin Fuster.

CIBERCV

In 2002, the ISCIII launched a funding scheme for thematic networks, with 3 networks dedicated to CVD research (RECAVA, REDINSCOR, and HERACLES). In 2012, the ISCIII decided to strengthen their cardiovascular research program by integrating these into 1 single network (Red de Investigación Cardiovascular, RIC). The RIC included 64 groups distributed in 7 specific research programs. With the restructuring of the thematic networks in 2017, the RIC was reformulated as a virtual research center, the *Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares* (Biomedicine Research Network Center for Cardiovascular Research; CIBERCV). With an annual budget of 3.28 million euros, the CIBERCV includes >480 researchers distributed in 40 groups from 24 institutions across Spain, with the groups selected through a competitive external evaluation based on scientific excellence. The CIBERCV provides more funding and greater flexibility than that of the previous networks and is organized into 4 dedicated research programs (myocardial damage, arterial disease, heart failure, and structural heart disease) and 2 transverse initiatives (biomarkers and epidemiology). More than 2 million euros are distributed to CIBERCV groups every year through a competitive internal procedure. Periodical evaluation is expected to generate a 5% to 10% turnover, facilitating the entry of emerging groups into the network.

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Disclosures

None.

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