

This is the peer reviewed version of the following article:

Lara-Pezzi E, Andres V, Fernandez-Aviles F, Fuster V, Ibanez B. Current State of Basic and Translational Cardiovascular Research in Spain. *Circ Res.* 2017;121(9):1036-9.

which has been published in final form at:

<https://doi.org/10.1161/CIRCRESAHA.117.310842>

News & Views:

Current state of basic & translational cardiovascular research in Spain

Enrique Lara-Pezzi^{1,2,3}, Vicente Andrés^{1,2}, Francisco Fernández-Avilés^{2,4}, Valentín Fuster^{1,5}, and Borja Ibáñez^{1,2,6}.

Affiliations: ¹ Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain; ² CIBER de Enfermedades Cardiovasculares (CIBERCV), Spain; ³ National Heart and Lung Institute, Imperial College London, United Kingdom; ⁴ Servicio de Cardiología, Hospital General Universitario Gregorio Marañón, Madrid, Spain; ⁵ The Zena and Michael A. Wiener CVI, Icahn School of Medicine at Mount Sinai, NY USA; ⁶ Department of Cardiology, Instituto de Investigación Sanitaria (IIS), Fundación Jiménez Díaz Hospital, Madrid, Spain.

Correspondence: Borja Ibáñez, Myocardial Pathophysiology Area, Centro Nacional de Investigaciones Cardiovasculares Carlos III & IIS-Fundación Jiménez Díaz. Melchor Fernández Almagro, 3, 28029 Madrid, Spain. Tel.: +34-914531200, Fax: +34 914531265, email: bibanez@cnic.es

Introduction

Although the risk of developing cardiovascular disease (CVD) is reduced by the Mediterranean diet¹, 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. 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. Basic and translational cardiovascular research groups have obtained around 300 competitive grants over the last 8 years, securing close to 50 million euros (Fig. 1A). Most national grants are awarded to one, or sometimes two, principal investigators and are usually small, ranging 80,000-120,000 euros for a 3 year project.

Over the last 15 years, the *Instituto de Salud Carlos III* (Carlos III National Institute of Health; ISCIII) 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 healthcare. The CVD dedicated network (CIBERCV) is discussed below in more detail. Another source of funding for CVD studies and training is the *Sociedad Española de Cardiología* (Spanish

Society of Cardiology; SEC). Grants from the SEC are small ($\leq 20,000$ euros per project), but the SEC funds a large number of projects every year.

Spanish cardiovascular research groups also receive significant support from international sources, with 50 groups awarded competitive international grants amounting more than 26 million euros over the last 5 years (Fig. 1B). 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, ITN), 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 programme) 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.

Publications

Despite the historical difficulties outlined above, Spanish cardiovascular research groups have a strong record in high impact publication. In the last 5 years, cardiovascular research groups published more than 2500 papers. Of these, 68% were published in journals with an impact factor in the first quartile and 29% of 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, in 2014 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, compared with 1.4 for all Spanish medical science papers in the same period. Consistent with these indicators, 29% of the 2500 papers were among the top 10% cited papers in their area, and more than 100 were among the top 1%. The citation distribution per paper is shown in Fig. 1C.

Almost two thirds of these articles were published in clinical journals, followed by journals specialized in molecular biology & genetics, biochemistry, pharmacology, and immunology (Fig. 1D). 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 (Fig. 1E).

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.

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)², led by the CNIC (see below). This study is a unique initiative in Spanish research, not only in terms of cohort size (n=4000), but also because of the deep patient phenotyping and the original funding scheme. 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 in order 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.

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)³, 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 two initiatives more than 10 years ago: the CNIC, a research center of excellence founded in 1999 and 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 by the Spanish Ministry of Health to tackle the CVD epidemic⁴. 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 leadership of Dr. Valentín 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). 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 (ERC) 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 (~800,000 euros per project). Landmark clinical trials arising from this highly successful CNIC-translational initiative included the PREDIMED¹ and METOCARD-CNIC trials⁵. CNIC also coordinates European initiatives that include the participation of many Spanish clinical centers, for example the SECURE and FOCUS trials⁶ within the “Fuster-CNIC-Ferrer” Cardiovascular polypill initiative led by CNIC General Director Valentín Fuster.

CIBERCV

In 2002, the ISCIII launched a funding scheme for thematic networks, with three networks dedicated to CVD research (RECAVA, REDINSCOR, and HERACLES). In 2012, the ISCIII decided to strengthen their cardiovascular research program by integrating these into one 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 2016, the RIC was reformulated as a virtual center, the *Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares* (Biomedicine Research Network Center for Cardiovascular Research; CIBERCV). The CIBERCV includes 40 Spanish 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 the previous networks, and is organized into 4 dedicated 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 5-10% turnover, facilitating the entry of emerging groups into the network.

Conclusions

Cardiovascular research in Spain was boosted in the last years thanks to national initiatives (launching the cardiovascular center of excellence CNIC, and creating research networks focused on CVD). Despite the economic constrains affecting the national budget dedicated to research, Spanish groups in the CVD field are becoming more competitive in the international (European) arena. Scientific output of Spanish CVD-dedicated groups is especially strong given the relatively small mean financial support per research group. The growing collaboration between basic and clinical researchers should further increase the competitiveness of Spanish consortia.

ACKNOWLEDGEMENTS

We thank Irene Maseda, Sara Fernández-Baillo, and Ana Fernández-Baza for help with the bibliometric analyses, and Simon Bartlett for English editing. The CNIC is supported by the Spanish Ministerio de Economía, Industria y Competitividad (MINECO) and the Pro-CNIC Foundation, and is a Severo Ochoa Center of Excellence (MINECO award SEV-2015-0505).

REFERENCES

1. Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, Martínez-González MA. Primary prevention of cardiovascular disease with a Mediterranean diet. *N. Engl. J. Med.* 2013;368:1279-1290
2. Fernández-Friera L, Peñalvo JL, Fernández-Ortiz A, Ibáñez B, López-Melgar B, Laclaustra M, Oliva B, Moco-roa A, Mendiguren J, Martínez de Vega V, García L, Molina J, Sánchez-González J, Guzmán G, Alonso-Farto JC, Guallar E, Civeira F, Sillesen H, Pocock S, Ordovás JM, Sanz G, Jiménez-Borreguero LJ, Fuster V. Prevalence, Vascular Distribution, and Multiterritorial Extent of Subclinical Atherosclerosis in a Middle-Aged Cohort: The PESA (Progression of Early Subclinical Atherosclerosis) Study. *Circulation.* 2015;131:2104-2113
3. Fernández-Avilés F, Sanz-Ruiz R, Climent AM, Badimón L, Charron D, Fuster V, Janssens S, Kastrup J, Kim H-S, Lüscher TF, Martin J, Menasché P, Simari R, Stone GW, Terzic A, Willerson JT, Wu J. Global Position Paper on Cardiovascular Regenerative Medicine. *Eur. Heart J.* 2017;Epub ahead of print.
4. Fuster V, Ibáñez B, Andrés V. The CNIC: A Successful vision in cardiovascular research. *Circ. Res.* 2016;119:785-789
5. García-Prieto J, Villena-Gutiérrez R, Gómez M, Bernardo E, Pun-García A, García-Lunar I, Crainiciuc G, Fernández-Jiménez R, Sreeramkumar V, Bourio-Martínez R, García-Ruiz JM, del Valle AS, Sanz-Rosa D, Pizarro G, Fernández-Ortiz A, Hidalgo A, Fuster V, Ibáñez B. Neutrophil stunning by metoprolol reduces infarct size. *Nat. Commun.* 2017;8:14780
6. Castellano JM, Sanz G, Peñalvo JL, Bansilal S, Fernández-Ortiz A, Álvarez L, Guzmán L, Linares JC, García F, D'Aniello F, Arnáiz JA, Varea S, Martínez F, Lorenzatti A, Imaz I, Sánchez-Gómez LM, Roncaglioni MC, Baviera M, Smith Jr SC, Taubert K, Pocock S, Brotons C, Farkouh ME, Fuster V. A polypill strategy to improve adherence: results from the FOCUS project. *J. Am. Coll. Cardiol.*;64:2071-2082

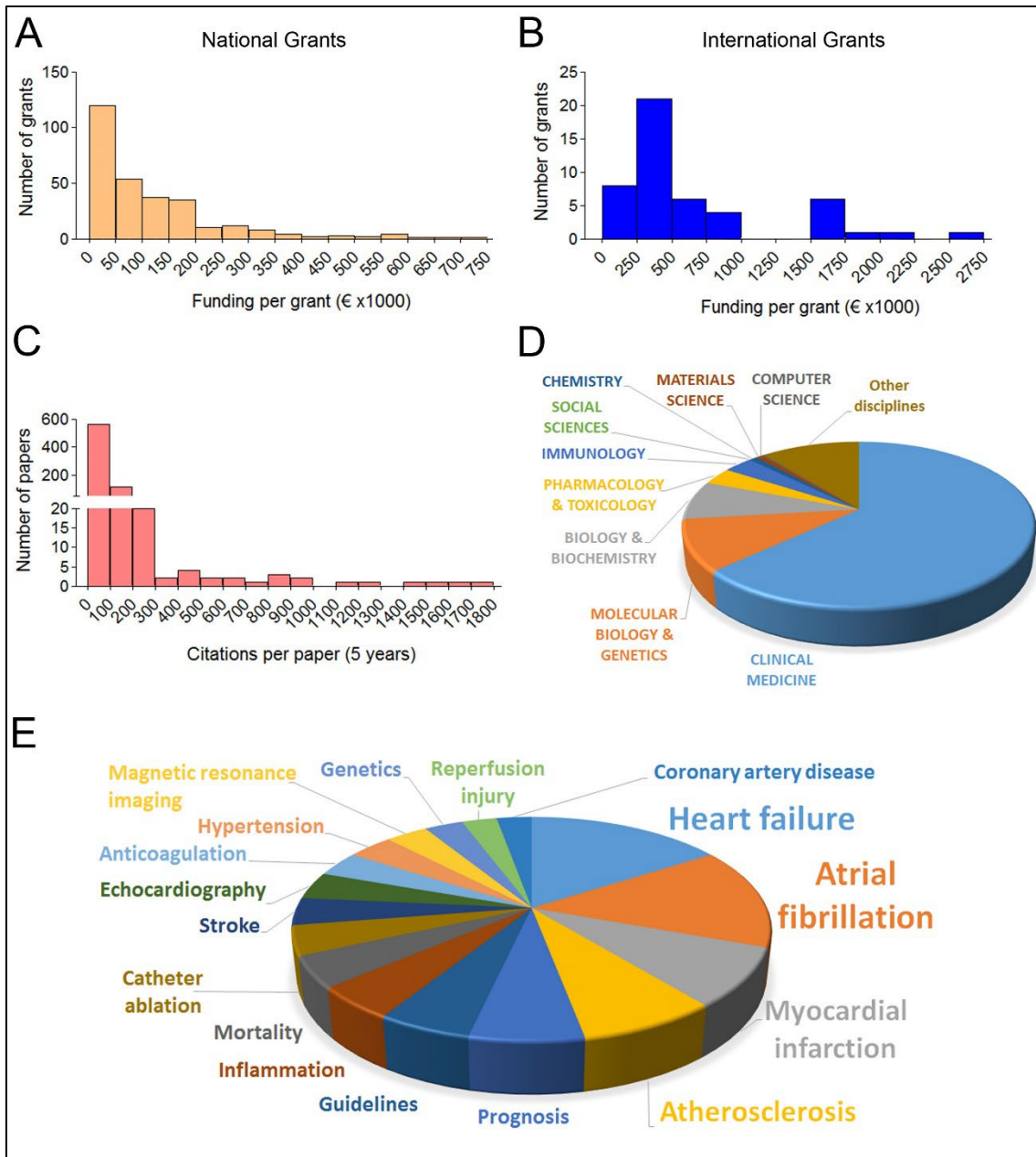


Figure. Active grants and publications in Spanish cardiovascular research, 2012 to 2016. **A** and **B**, Distribution of national (**A**) and international (**B**) grants awarded to Spanish cardiovascular research groups. For network grants, the funding share corresponding to each Spanish group was 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.