

Editorial

(Collaborative) cardiovascular research in Spain: quo vadis?

Investigación cardiovascular (colaborativa) en España, ¿quo vadis?

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Spain has a long tradition in basic biomedical research and translational science, with notable results in the neurosciences, molecular biology, immunology, and oncology. However, the main cause of mortality in Europe and Spain is cardiovascular disease. To face this paradox *Instituto de Salud Carlos III* (Carlos III Health Institute) launched 2 ambitious country-wide initiatives at the start of the 21st century, focused on the creation of a large cardiovascular research center and enhancement of network-related cardiovascular research infrastructures.¹ These initiatives arose from a collective impulse: the pursuit of multidisciplinary, broad-based activity and above all, interaction. Despite the undeniable impact of the great recession of 2008 to 2016, both these initiatives have maintained their funding and now comprise the 2 main pillars of cardiovascular research in Spain.

Created in 1998, the *Centro Nacional de Investigación Cardiovascular* (CNIC; Spanish National Center for Cardiovascular Research) has become consolidated in the eyes of world as a center of excellence.² With effective preclinical and translational research, it has carried out projects such as PESA,³ METOCARD-CNIC,⁴ REBOOT (NCT03596385), and the SECURE study (NCT02596126), cohort clinical trials involving applied clinical research of recognized importance. The CNIC has been remarkably successful in obtaining competitive research funding from international sources, and through the Pro-CNIC Foundation, it is an example of patronage management in science.

The *Centro de Investigación Biomédica en Red* (CIBER, Biomedical Research Networking Center) began in 2006 with several centers which were assembled in a single group in 2013. Since the establishment of collaborative research networks, CIBER has advanced the policy of *Instituto de Salud Carlos III* in promoting multicenter research. The PREDIMED⁵ and PREDIMED-PLUS⁶ programs, coordinated by researchers from the subject area of obesity and nutrition (CIBEROBN), are paradigmatic examples of CIBER's value. With the use of clinical trial designs, the PREDIMED studies have been crucial for establishing the Mediterranean diet as a worldwide reference in nutrition. Cardiovascular research was incorporated in the CIBER Consortium as a separate subject area (CIBERCV) in 2017. Arising from the *Red de*

Investigación Cardiovascular (RIC; Cardiovascular Research Network),⁷ CIBERCV includes 40 competitively selected clinical and preclinical research teams. In its 4 years of existence, CIBERCV has devoted considerable efforts to strengthening research groups, fostering interaction, promoting cardiovascular research training, and enhancing alliances for participation in international projects.¹

It is still too early to analyze the results of these measures, although important advances are already in sight. In a recent article published in *Revista Española de Cardiología*, Chorro et al.⁸ used bibliometric techniques to analyze interactions between Spanish research groups and institutions in 8 cardiovascular research topics. Through an analysis of authorship and collaboration, the authors drew a map of the interactions occurring in topics such as catheter arrhythmia ablation, cardiac resynchronization, drug-eluting stents, direct anticoagulants, sacubitril-valsartan use, stress cardiomyopathy, percutaneous valve implantation, and microRNAs. Useful conclusions can be derived from this study regarding the strengths and weaknesses of cardiovascular research in Spain. Some of the findings described by Chorro et al.⁸ are discussed below, and the challenges and opportunities they present for the coming years are summarized.

The most frequent interactions identified by Chorro et al.⁸ occur between institutions linked by close official alliances. Typically, academic teams perform research in hospitals, and their researchers have a dual affiliation with the hospital and university. Dual affiliation of a single team undoubtedly confounds analyses of scientific interactions, and it may seem artificial. However, scientific quality and impact are closely linked to multidisciplinary activity, and collaborations between hospitals and universities are optimal for this purpose. Based on this premise, *Instituto de Salud Carlos III* created the *Institutos de Investigación Sanitaria* (Health Research Institutes) in 2001, using the existing alliances between universities and health care centers as the mainstay. The Institutes, which are subject to rigorous auditing and re-accreditation, provide support structures and scientific-technical platforms, and are powerful instruments to fortify the research carried out in hospitals.

Nonetheless, interactions between the educational and health care settings require an even greater effort. The current medical training model in Spain is upheld by the figure of the university professor, who is usually associated with the publically-funded Spanish National Health System. This model has a strictly educational intent, and there is no equivalent mechanism with scientific objectives. The recently implemented biomedical

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degrees (biology, bioengineering, biotechnology, etc) provide an excellent opportunity to integrate teachers and researchers from nonhealth-related professions into the National Health System. These individuals should have channels beyond the initial incentives in this line (eg, the *Instituto de Salud Carlos III* Sara Borrell and Miguel Servet programs) to attain definitive consolidation within the hospital setting. In the opposite direction, an *ad hoc* policy should recognize the value of research performed by health professionals. An academic career may quickly become unattractive for new generations of health professionals,^{9,10} which would pose a serious threat to sustaining hospital research at mid- and long-term. Coverage of teaching positions in some specialties is at risk in Spain for the want of candidates with sufficient scientific experience to meet requirements for accreditation as university professors. Changes are needed in the current legal framework to make the employment relationship compatible in the National Health System, universities, and national research centers. In this way alone can multidisciplinary interactions be enriched to their full potential, enabling access of nonmedical professionals to applied medical research and incorporating new generations of health professionals into basic research.

Another notable result reported by Chorro et al.⁸ concerned the time elapsed between emergence of one of the study topics and publication on the topic by Spanish researchers. The analysis found a mean time delay of 4 years. This result is worrisome, as it shows that most Spanish contributions took place in the postmarketing phase of the analyzed techniques (catheter ablation), drugs (sacubitril-valsartan), and devices (drug-eluting stents and percutaneously implanted prostheses). Despite the increasing volume of our preclinical research, the areas examined did not make substantial contributions in basic science, proof of concept, prototypes, or initial phases of clinical trials. The subjects chosen for study by Chorro et al. may not be representative of the total of cardiovascular research, but this finding is consistent with the reported weaknesses in terms of innovation and transfer to market affecting all Spanish research.¹¹

CHALLENGES AND OPPORTUNITIES (2021-2026)

The COVID-19 crisis has caused an unprecedented upheaval in the appraisal of biomedical research. Coinciding with the publication of this article, the Spanish Recovery, Transformation, and Resilience Plan,¹² which will affect our future scientific strategies, is being discussed in Brussels. The general lines of the European Union's new investment and research plan are encompassed in the Europe Horizon program,¹³ and several national strategies have been aligned with it. This is an excellent chance to associate the capability of Spain with the opportunities provided by this new framework.

Endowed with a budget of €95.5 billion, Europe Horizon is the key research funding program for the entire European Union until 2027. It is remarkable that Europe Horizon specifies cancer, and not cardiovascular disease, as the single mission dedicated to the life sciences.¹⁴ Several factors likely contribute to this, such as preclinical research transferability and differing social perceptions of the health impact of one specialty or another. As regards innovation, the number of new molecules and drugs under development by pharmaceutical companies is clearly smaller for cardiovascular treatment than for antitumor treatment or immunomodulators. However, the areas requiring interventions in the Europe Horizon health cluster include environmental pollution, noncommunicable diseases, digital health, and mitigating the effects of ageing, and cardiovascular health seems to be an essential component in all of these. Therefore, cardiovascular

research in Spain must be well aware of these directions to be competitive in Europe.

Over the last few years, Spain has vigorously promoted academic clinical trials. Through the Strategic Action in Health effort in 2018, *Instituto de Salud Carlos III* resumed publicly-funded research in clinical trials and advanced therapies in areas where support by the pharmaceutical industry is not profitable. Cardiovascular research is particularly interesting for this type of initiative and several projects have been funded in this area. The efficacy of colchicine for preventing heart failure decompensation (NCT04705987) and the value of adrenergic block for imaging assessment of systolic function (pending NCT) are examples of randomized clinical trials made possible by this initiative.

In 2020, the Spanish Cardiology Society launched the ECAM-SEC program, aimed at funding high-impact multicenter clinical trials in Spain. With an endowment of €1 million, it is the most ambitious private initiative devoted to independent cardiovascular research. The BA-SCAD study (NCT04850417) will use a factorial randomized clinical trial design to determine the best secondary prevention approach for patients experiencing spontaneous coronary artery dissection.

The worldwide effort to advance precision medicine by combining clinical information with omic, phenotypic, and environmental exposure data is particularly striking. Cardiovascular medicine lags far behind oncology in this regard and, with certain exceptions, a large part of heart disease diagnoses are generic and syndromic.¹⁵ Prevention measures known to be effective (eg, diet, physical activity) are undoubtedly of a general nature, but most pharmacological treatments and interventions are also aimed at large diagnostic groups with little individualization. Over the last decade, various population studies have been conducted around the world to clarify the association between phenotypic heterogeneity and cardiovascular disease. Big data analysis from several cohorts—the Framingham Heart Study, the Nurses' Health Study, the CHARGE consortium, SWEDEHEART, and UK BIOBANK—have led to important advances in determining the individual mechanisms of hypertension, coronary disease, and acute myocardial infarction. Other, even more ambitious initiatives, such as the Million Veteran Program and the All of Us study, funded by the United States National Institutes of Health, have provided important evidence in this regard.¹⁵ Rather than another option, precision medicine is a necessity to improve prevention and treatment of cardiovascular disease.¹⁶

Spain is doing its utmost to remain competitive in precision medicine. The Spanish Strategy for Science, Technology, and Innovation (2021-2027) includes a huge effort aimed at improving the effectiveness of our researchers in this area.¹⁷ As in Horizon Europe, cardiovascular health is not specified among its lines of action, but they do include precision medicine, new diagnostic and therapeutic techniques, and ageing. In keeping with this strategy, *Instituto de Salud Carlos III* launched a call for grants in precision medicine infrastructure for 2021. Considerable resources have been devoted to generating population cohorts and powerful platforms for genetic sequencing and data analysis from electronic medical records. Cardiovascular research should take advantage of these resources by presenting original proposals.

In this regard, the CIBERCV cardiovascular research area provides an ideal platform to attune research activity to the capabilities of its research teams. In 2021, CIBERCV implemented a dedicated series of strategic projects to optimize collaboration in coordinated monographic programs. Led by the heads of the CIBERCV scientific lines, the ultimate objective is to develop and execute an ambitious project that incorporates basic knowledge, epidemiology, data science, biotechnology, and holistic clinical research (which includes the patient as an active participant in decision-making) to the setting of precision medicine in heart failure. By harmonizing

observational cohorts with population cohorts and *ad hoc* designed clinical trials, a complete scope of collaborative research can be established with the purpose of mitigating the impact of the common end path of most heart diseases.

In summary, the postpandemic scenario poses major challenges and opens up enormous opportunities for precision cardiovascular research in Spain for the next 6 years. The ongoing transformations in health organization, digitization, current knowledge, and telemedicine are converging to change the model (healthcare and productive), and this trend should enhance biomedical research. From the European Union to national and regional governments, scientific societies,¹⁸ and the sphere of industry, excellent opportunities are in sight for Spain, and our cardiovascular research structures are sufficiently developed to take advantage of them with guaranteed success. Through ambitious collaborative projects, now is the time for our researchers to step up and respond to the current and future global challenge posed by cardiovascular disease.

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CONFLICTS OF INTEREST

There were no conflicts of interest related to this article.

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