

Editorial

CNIC: Achieving Research Excellence Through Collaboration

El CNIC: investigación de excelencia basada en la colaboración

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INTRODUCTION

The *Centro Nacional de Investigaciones Cardiovasculares Carlos III* (CNIC) represents a new model of cardiovascular research, in which emphasis is placed on close collaboration between basic and clinical researchers, both nationally and internationally, and on creating a network of relations with clinical institutions that will enable acquired knowledge to be efficiently transformed into real health benefits for society. Despite its relatively short history, the CNIC, thanks to the collaborations established with partner institutions, has demonstrated leadership and singular excellence in several key areas of research, training and discovering of future talents which has recently been recognized by the "Severo Ochoa Centers of Excellence Program".

CENTRO NACIONAL DE INVESTIGACIONES CARDIOVASCULARES CARLOS III AND ITS MISSION

The public research institute CNIC, an autonomous center within the *Instituto de Salud Carlos III*, was founded in 1999 by the Spanish Ministry of Health. In December 2005 the Spanish government signed an agreement with a core group of leading Spanish private companies and foundations to establish the Pro-CNIC Foundation, dedicated to financing and promoting the CNIC's activities. With the inauguration of the CNIC's purpose-built research facilities in February 2006, the center was re-launched with a new leadership and a mission to improve cardiovascular health in the general population by generating scientific knowledge, efficiently translating that knowledge to the clinic, and providing new researchers with a comprehensive training.^{1,2} The center was structured into new scientific departments, and an intensive recruitment program was launched in 2007. The CNIC today remains a young, growing institution, with 72% of the current faculty recruited since 2007 and 33% since 2009. The new mission established for the CNIC also required the remodeling of some 5000 m² of the CNIC building and satellite units to host the new programs.

To accomplish its new mission, the CNIC has defined three priority areas:

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1. *Excellence in research*, achieved by conducting and promoting high-quality and high-profile basic, clinical, and population research in the cardiovascular area. The CNIC ensures research excellence through the evaluation and analysis of all its scientific activities by an external committee, the scientific advisory board, composed of 13 senior figures from some of the most prestigious international research institutions. The scientific advisory board ensures that high-quality criteria are applied to the unbiased critical evaluation of CNIC results, scientific programs and production, and training policies.
2. *Efficient translational medicine*, achieved by promoting the translation of knowledge from basic research to patient care and public health in collaboration with Spain's National Health System and scientific societies, as well as by conducting translational research with potential application in the pharmaceutical and biomedical industries.
3. *Training*. Since its creation, the center has made exceptional efforts toward identifying and training the best and brightest talents for cardiovascular research. This effort is coordinated under the umbrella of the center's comprehensive training program, the CNIC-JOVEN Training Plan, which covers all levels from secondary education through to the training of post-doctoral fellows and medical and scientific professionals.³

CENTRO NACIONAL DE INVESTIGACIONES CARDIOVASCULARES CARLOS III AND ITS INFRASTRUCTURE

To achieve the CNIC's objectives, the center's research has been organized into three departments which study areas of fundamental interest identified as the most likely to lead to rapid advances in medical practice:

- Vascular Biology and Inflammation
- Cardiovascular Development and Repair
- Epidemiology, Atherothrombosis and Imaging

These research departments work closely with the Translational Platform, which coordinates intellectual property management and the translation of new knowledge into improved clinical practice and public health.

The center benefits from state-of-the-art facilities that ensure top-quality technical support for its scientific projects including



Figure 1. Dr. Valentín Fuster, *Centro Nacional de Investigaciones Cardiovasculares Carlos III* General Director, receiving the “Severo Ochoa” Award from the Spanish Minister of Science and Innovation.

specialized units for Genomics, Cellomics (cytometry and high content screening), Proteomics, Microscopy, Gene Targeting, Transgenesis, Viral Vectors, Pluripotent Cell Technology, and Bioinformatics. For research involving animals, the CNIC has one of the most modern Animal Facilities in Europe which houses small (zebra fish, mice and rats), medium (rabbits) and large (pigs) animal models for cardiovascular studies. The CNIC has also created a new platform (imaging facility) devoted to the most advanced in evolving multimode cardiovascular imaging techniques including nuclear magnetic resonance imaging (MRI), positron emission tomography (PET), ultrasound, bioluminescence, and fluoroscopy.

CENTRO NACIONAL DE INVESTIGACIONES CARDIOVASCULARES CARLOS III AND THE “SEVERO OCHOA” AWARD FOR INVESTIGATION

The “Severo Ochoa Centers of Excellence Program” was launched in 2011 by the Spanish Ministry of Science and Innovation, to reward and promote outstanding research output

and practice by Spanish centers, as determined by international standards. The evaluation and selection committees were composed of leading international experts from 12 countries, and the subcommittees were chaired by a Nobel laureate in each of the three disciplinary categories: Life Sciences, Physics and Engineering, and Social Sciences and Humanities. Of the 75 initial applicants, eight centers were awarded this prestigious accolade, with the CNIC one of just three centers in the Life Sciences category receiving the award (Figs. 1 and 2).

During the first stage of the Severo Ochoa evaluation, the CNIC was able to demonstrate key characteristics of scientific excellence such as a high-quality research production, an appropriate environment for supporting excellent research and its dissemination, and an active policy for attracting and training the best young researchers from across the globe. In the second stage, the CNIC, as a pre-selected center, presented a basic and translational research program based on the development of advanced imaging technologies for the early diagnosis and prevention of cardiovascular disease. The CNIC’s program identifies three areas of innovative research.

New Generation Imaging Studies

The CNIC has established a strategic alliance with Philips to explore the potential of new fusion imaging techniques (PET/computed tomography [CT], PET/MRI) and magnetic particle imaging to improve detection of subclinical atherosclerosis. Moreover, a linked program will design and develop imaging probes and radio-ligands for use in anatomical and functional PET/CT imaging of atherosclerotic lesions in pig models, including transgenic minipigs that develop extensive human-like coronary atherosclerotic lesions. A portfolio of relevant specific cardiovascular targets has already been identified by CNIC groups, and new targets will be added during the “Severo Ochoa” research program.

New Generation Imaging-based Translational Research in Population Studies

Imaging research studies will be conducted on a large population of patients with extensive anterior wall myocardial



Figure 2. Dr. Miguel Torres (second from the left) *Centro Nacional de Investigaciones Cardiovasculares Carlos III* Associate Director, with the Spanish Minister of Science and Innovation and directors from the other seven awarded centers.

infarctions (MI). The CNIC has developed novel imaging sequences able to map not only the infarcted tissue (fibrosis) but also the border zone myocardium, where the fatal arrhythmias are initiated. By performing serial MRI studies we will be able to longitudinally map fibrotic tissue homeostasis and study the correlation with arrhythmia incidence, eventually leading to a novel paradigm for risk stratification in MI patients. Since myocardial salvage strongly depends on the mitochondrial response to ischemia/reperfusion, CNIC groups specialized in myocardium and tissue homeostasis and repair will assess whether patients' clinical and imaging data correlate with mitochondrial DNA sequence, thus exploring new potential correlations between mitochondrial genetics and tolerance to ischemia/reperfusion.

The CNIC is currently running two large longitudinal studies to detect subclinical vascular lesions and their progression: *a)* Progression of Early Subclinical Atherosclerosis project in partnership with Banco Santander and the Botín Foundation; and *b)* Aragon Workers Health Study with employees at the General Motors car plant in Zaragoza. Selected individuals with subclinical atherosclerosis from these ongoing CNIC population studies will be recruited into MRI/PET multimodality imaging tests designed to explore new frontiers in the detection of atherosclerosis burden and inflammation.

Exploring New Cardiovascular Disease Mechanisms in New Generation Imaging/Population Studies: Aging Pathways

The CNIC's ongoing large population studies provide a unique resource for testing hypotheses of major biological and medical relevance to the field of cardiovascular research, such as the involvement of aging pathways in atherosclerosis progression and the role of microcirculation alterations in age-related brain degeneration.

A link has been established between short leukocyte telomere length (LTL) and atherosclerosis. However, most epidemiological studies were cross-sectional and relied on small cohorts. Given the high inter-individual variation in LTL, longitudinal studies of LTL with image analysis of disease progression are needed to verify this hypothesis and assess whether disease correlates with initial LTL, the shortening rate, or both. LTL will be measured at baseline and at 6-year follow-up in samples from individuals enrolled on CNIC population studies and correlated with cardiovascular disease progression. The study will also examine single nucleotide polymorphisms in known and suspected LTL-regulating genes.

Another key area is the potential connection between cardiovascular disease, LTL ablation, and progerin expression. Progerin is a mutant form of lamin produced by the aberrant splicing that causes Hutchinson-Gilford Progeria syndrome, a disease characterized by accelerated LTL shortening and atherosclerotic cardiovascular disease. Remarkably, normal aging is associated with progressive accumulation of progerin in the artery wall and other tissues, and recent *in vitro* studies demonstrate that telomere attrition activates progerin production. The relationship between LTL and progerin in this potent human study will establish the role of this aging pathway in cardiovascular disease and promises new diagnostic and prognostic tools. In addition, the aging pathway studies will be coordinated with new generation imaging studies of the brain, with the aim of determining the role of microvasculature in age-related brain degeneration.

The CNIC's "Severo Ochoa" program will have a major positive impact on biomedicine, not only because improved non-invasive imaging techniques will allow rapid, non-disruptive diagnosis, but also because these methods are increasingly valuable for basic and preclinical studies, clinical research, and population studies. The

high sensitivity of these imaging modalities is especially relevant to cardiovascular disease since this disease typically progresses silently for many years before symptoms appear. Thanks to strategic alliances and close collaborations with clinical institutions, the CNIC has established an advanced imaging infrastructure and biomedical resources that position the center at the international forefront of new generation imaging development and its application to diagnosis, prognosis, prevention and mechanistic understanding of cardiovascular disease.

CENTRO NACIONAL DE INVESTIGACIONES CARDIOVASCULARES CARLOS III: EFFICIENT TRANSLATION AND EDUCATION THROUGH COLLABORATION WITH THE SPANISH NATIONAL HEALTH SYSTEM

The central aim of biomedical research is to translate knowledge generated in basic research laboratories into improved and innovative clinical practice, and reciprocally to stimulate research into questions raised in healthcare centers. Excellence in this area therefore requires close contact with clinical institutions. Aware of this, the CNIC has established a strategic network with institutions within the Spanish National Health System (Fig. 3) and collaborations with the Spanish Society of Cardiology (SEC, *Sociedad Española de Cardiología*) to develop translational research projects and to identify and train the best investigators for these types of projects.

Translational Grants

To foster these contacts, in 2007, the CNIC set up a specific program of grants to finance translational research projects (Translational Grants) in the field of cardiovascular diseases. A major goal of this program is to cement bidirectional links between the CNIC's basic researchers and researchers working in the Spanish National Health System. Since the program's launch, the CNIC has financed eight translational projects, involving 28 institutions from Spain and abroad, including eight Spanish hospitals.

METOCARD Project

Another key CNIC goal is to build its own translational research program. The CNIC's work in this area places it as a leader in the identification and clinical investigation of molecular and physiological factors that influence cardioprotection during MI. Models of MI have been established in rodents and large animals and are used to study the mechanisms underlying the beneficial effects of various cardioprotective strategies.⁴ In close collaboration with nine Spanish hospitals and medical emergency services, we are coordinating a clinical trial based on pre-clinical research performed by CNIC groups (METOCARD Project). The trial uses state-of-the-art non-invasive imaging technology (MRI) to evaluate the effectiveness of a cardioprotective strategy based on beta adrenergic modulation in the ambulance within the first 2–4 h in patients with MI. This study is the largest clinical trial into acute MI (AMI) that uses MRI as its main endpoint. We are also investigating circadian oscillations in myocardial tolerance to ischemia/reperfusion, building on our recent demonstration that the response of the human heart to AMI varies with the time of day.⁵ We are currently using animal models to study the mechanisms responsible for this circadian variation, in order to find a pharmacological surrogate that can be translated to human care.



Figure 3. Centro Nacional de Investigaciones Cardiovasculares Carlos III collaborations with the Spanish National Health System. Total number: 63. CNIC: Centro Nacional de Investigaciones Cardiovasculares.

Centro Nacional de Investigaciones Cardiovasculares Carlos III-Banco Santander and Botín Foundation Progression of Early Subclinical Atherosclerosis Project and Aragon Workers Health Study Project

The CNIC also conducts translational research based on large-population longitudinal studies that use cutting edge non-invasive imaging technology for atherothrombosis prediction. The center leads and coordinates two large population-based studies aimed at identifying predictive factors and strategies to recognize subclinical cardiovascular alterations: the Progression of Early Subclinical Atherosclerosis project and the Aragon Workers Health Study. More than 9000 apparently healthy individuals in Madrid and Zaragoza are being enrolled on these studies. These individuals are being stratified for classical risk factors in parallel with cutting-edge imaging studies (3-dimensional vascular ultrasound, CT scan for calcium scoring, and MRI/PET) and “omics” analysis in collaboration with the *Hospital Carlos III de Madrid* and the *Instituto*

Aragonés de Ciencias de la Salud. Biological samples will be stored in the CNIC biobank. Clinical, imaging and biological studies will be repeated in the study populations at 3 and 6 years of follow-up. These studies will permit the identification of predictive factors of cardiovascular disease and thereby allow the design of specific preventive strategies. These projects have already attracted external funds of near 25 million euros. These studies are complemented by basic research in animal models aimed at identifying the cellular and molecular risk factors of atheroma plaque formation.⁶

Centro Nacional de Investigaciones Cardiovasculares Carlos III-FERRER Polypill/FOCUS Project

Another main translational project at the CNIC is the development of a polypill for chronic cardiovascular patients.⁷ With this project, the CNIC is not only likely to have an immediate positive

impact on patient health, but will also obtain an economical return on its activities that will begin to compensate for the public investment in the center. The burden of cardiovascular disease is increasing steadily, particularly in low and middle-income countries. The use of a fixed-dose combinations pill, the so-called “polypill”, has been proposed as a means of improving cardiovascular prevention by reducing cost and increasing patient adherence to treatment.⁸ Since 2006 the CNIC has been working with the pharmaceutical company FERRER to develop the CNIC-FERRER polypill (Trinomia[®]), containing acetyl salicylic acid, simvastatin and ramipril. Trinomia[®] is now commercially available in Guatemala and is in the process of registration in other Central and South American countries. We are currently conducting a clinical study called FOCUS, funded by the 7th Framework Programme of the European Commission, that will help us to understand the factors that determine poor treatment adherence and inappropriate prescribing for secondary cardiovascular prevention in populations from two countries in Europe–Spain and Italy–and three in South America–Argentina, Brazil and Paraguay. The Spanish clinical trial will be run in collaboration with 20 primary healthcare centers.

IMJOVEN Project

The CNIC is also involved in the study of the risk factors for AMI in young women (IMJOVEN Project). IMJOVEN is the Spanish counterpart of the VIRGO study,⁹ an National Institutes of Health-sponsored investigation led by Dr. Harlan Krumholz of Yale University into the excess risk in young women with AMI, aimed at identifying demographic, clinical, metabolic, psychosocial, health-care delivery, and biological determinants of prognosis. IMJOVEN will include 450 patients (300 women and 150 men) with a previous history of AMI and use the same protocol as the VIRGO study. Recruitment has already been accomplished and patients have been included in 24 hospitals in Spain. The project involves groups from the CNIC, the SEC (Working Group on Ischemic Heart Disease and Coronary Care Units), and the RECAVA and HERACLES National Cooperative Research Networks (*Redes Temáticas de Investigación Cooperativa*).

National Cooperative Research Networks also provide the framework for CNIC collaborations aimed at supporting translational research in the biomedical field. These collaborations currently involve more than 60 CNIC investigators in two of these networks, RECAVA and TERCEL.

Training Programs and Mobility

Translational biomedical research needs highly qualified personnel, trained in both medicine and research. The CNIC, in collaboration with national and international institutions, has designed a comprehensive training plan, structured in 12 specific programs, to help medical professionals develop mixed professional careers. Moreover, through its flexible human resources program the center has created part-time research positions that allow investigators to combine research and clinical activities.

Based on a very successful experience in the United States,^{10,11} and in collaboration with the SEC, the CNIC runs the annual Jornada Cicerone, a two-day workshop, under the banner “Everything you need to know about cardiovascular research” which provides career guidance for tomorrow’s cardiovascular investigators. Both institutions also offer a course on Cardiovascular Pathophysiology which provides an opportunity for physicians to “retool” themselves with new knowledge and approaches to cardiovascular research. Survey data show that around 80% of attendees consider these workshops of vital importance in planning their future

careers as investigators and for keeping them updated on developments in cardiovascular research.

With the aim of promoting translational research not just at the CNIC but also in Spanish clinical institutions, the center has established three flagship programs to attract young medical professionals to research and generate bridges between the CNIC and clinical institutions. The INVESMIR Program is intended to help participating resident interns to establish contacts and collaborations at the CNIC that will support them, after completion of their medical intern residency specialization training, in pursuing their own research projects within the hospitals of the Spanish National Health System. The CARDIOJOVEN Program offers Spanish hospital physicians a high quality and broad training in cardiovascular research over a 2-3 year period. This includes periods at the Johns Hopkins University, the CNIC laboratories in Madrid, and other centers. At the end of this training, physicians return to their home institution with a commitment to devote part of their time to cardiovascular translational research in collaboration with the CNIC. With a similar commitment, based on an agreement with the Mount Sinai School of Medicine (MSSM), the CARDIO-IMAGE Program offers Spanish scientists, ranging from graduates to established cardiologists, a blue-ribbon training in state-of-the-art cardiovascular imaging at the CNIC-MSSM Joint Unit in New York.

Through these programs and collaborations, the CNIC is creating a strong base of talented and expertly trained researchers, capable of leading high quality cardiovascular translational projects. Over 900 people have participated in the CNIC workshops, and 25 medical professionals have enrolled on the training programs. Furthermore, the CNIC’s open human resources program has brought around 30 professionals from the Spanish National Health System to work on translational projects at the CNIC through stable part-time positions and collaboration agreements. These initiatives place the CNIC in a privileged position from where it can tackle ambitious and challenging translational research projects.

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CONFLICTS OF INTEREST

None declared.

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