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The CNIC: A successful vision in cardiovascular research

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The “Centro Nacional de Investigaciones Cardiovasculares Carlos III, CNIC” (*National Center of Cardiovascular Investigation*), in Madrid, Spain, has rapidly established itself as a leading international center for cardiovascular research through pioneering leadership and a research strategy that cuts across disciplinary boundaries.

Mission and leadership

Over the past 10 years, the CNIC has built an unrivalled infrastructure and a powerful, cross-disciplinary research base that embraces multiple disciplines and both population and patient studies. One of the keys to this achievement is the commitment of national government to building a flagship research institute to tackle the cardiovascular disease (CVD) epidemic. But the public purse is only part of the story; most importantly the CNIC is funded through an innovative public-private financing structure which injects not only added financial security but also the wide-ranging business and management expertise of some of the most prominent Spanish businesses (Pro CNIC Foundation, see below).

The other key ingredient underpinning the CNIC’s success is a clear and consistently applied vision, at the heart of which is a shift from an emphasis on clinical events (the current paradigm) to the identification of CVD in its preclinical stages (the new paradigm pursued by the CNIC). This vision brings a cohesive strategy that embraces public health promotion, research infrastructure, professional training, and a clear focus on close collaboration between basic and clinical researchers to ensure that acquired knowledge is translated into real health benefits. This vision is brought to reality through an agile management structure that promotes training and the exchange of ideas and expertise, a comprehensive modern infrastructure of technical units and support services, and above all a young, energetic team of scientists, clinicians, and technicians dedicated to advancing knowledge about and treatment of CVD.

The Center’s strategic direction is defined by CNIC Director Valentin Fuster, who currently combines functions as General Director of the CNIC and Director of the Cardiovascular Institute and Physician-in-Chief at the Mount Sinai Medical Center, New York. Dr. Fuster, who comes to the CNIC once a week, brings to the Center his vast leadership experience across the spectrum of CVD research and prevention.

Dr. Fuster’s vision and leadership are directly supported by two senior investigators who run the Basic Research Department (Vicente Andrés) and the Clinical Research

Department (Borja Ibañez). This scientific triangle is the cornerstone of the Center's development and success.

Dr. Andres is a basic scientist with a translational approach who has a long internationally-recognized scientific career. He is also Full Professor in the Spanish National Research Council and counts with a vast experience in science management and leadership.

Dr. Ibañez, who works part-time as a clinical Cardiologist at the top-ranked Fundación Jiménez Díaz University Hospital, brings to the Center his knowledge and expertise in imaging, preclinical models and to conduct the clinical and translational research activities of the CNIC.

A short history

The CNIC was founded in 1999 by the Spanish Ministry of Health. Problems in stabilizing the CNIC leadership early on led to the freezing of recruitment and development until December 2005. Coinciding with the arrival of Dr. Fuster as CNIC Director in 2005, the Spanish government signed an agreement with a group of leading Spanish companies and charitable foundations to establish the Pro CNIC Foundation, dedicated to financing and promoting the CNIC's activities. The Center is thus financed through direct governmental core funding, the private sector through the Pro CNIC Foundation, and competitive grants. The CNIC building opened in July 2005 (Figure 1). This modern facility covers a total floor space of 23,000 m² and was equipped from the outset with the latest scientific equipment and core facilities.

The Center's new vision required extensive strategic revision, including the launching of new research areas and the introduction of 5-yearly independent evaluations of all researchers. The CNIC remains a young, growing institution, in which 72% of the current faculty joined since 2007. The Center's new direction also required the remodeling of more than 3000 m² of the CNIC building to host the new programs. . The new facilities became fully operational in 2012.

Despite its short history, the CNIC has excelled in several key areas of research, training and talent discovery. This progress was recognized in 2011 by the Severo Ochoa Centers of Excellence Program (Figure 1). This program sponsored by the Spanish government rewards and promotes outstanding research output by Spanish Centers. The CNIC was then one of the three Centers in the Life Sciences category to receive the first award in 2011, which was recently renewed for the period 2016-2019.

Dynamic organization and technological innovation

The CNIC pursues its goals through 3 linked strategic arms: excellence in research, training, and translation into CVD prevention and treatment. For the CNIC, "excellence in

research” means conducting and promoting high-quality and high-profile basic, clinical, and population research. To ensure objective assessment of the Center’s research output and direction, all scientific activities are evaluated by the Scientific Advisory Board, an external body composed of 13 senior figures at some of the most prestigious international research institutions. The board evaluates CNIC researchers’ performance every year according to an up-or-out system and makes recommendations about the recruitment of new group leaders.

The CNIC is organized to maximize collaboration between basic and clinical researchers and to encourage networking with hospitals so that acquired knowledge can be efficiently transformed into health benefits. To foster closer interaction between clinical and basic researchers, the CNIC was restructured in 2015 into two interconnected research departments, Basic Research and Clinical Research. Under the umbrella of this balanced scientific leadership, 6 interconnected multidisciplinary programs are grouped into 3 Research Areas (Figure 2), each coordinated by one basic and one clinical researcher: Vascular Pathophysiology Area (coordinating programs in Vascular Biology and Signaling & Inflammation), Myocardial Pathophysiology Area (Myocardial Biology and Cardiovascular Metabolism programs), and Cellular & Developmental Biology Area (Genetics & Development and Cell Biology & Physiology programs) (Figure 2).. The 29 CNIC research groups are strategically distributed, with each Area including basic and clinical researchers. Clinical work, data acquisition, statistics and analysis are developed with the support of specialized core facilities. Large-population clinical studies are conducted by groups from different Areas, often in collaboration with national and international partners (see below), and coordinated by Dr. Fuster. From our experience, this multidisciplinary approach is strengthening connections and increasing synergies among different research groups.

Advances in scientific knowledge and clinical practice are driven by technological innovation, and the CNIC has from the outset built strength in leading-edge technologies. CNIC researchers can take advantage of these technologies without diverting their own resources thanks to state-of-the-art Technical Units that ensure top-quality technical support. The Technical Units comprise Genomics (specialized in second generation sequencing NGS technologies), Cellomics, Proteomics/Metabolomics, Microscopy, Pluripotent Cells and Transgenesis (CRISPR/Cas9 technology), Viral Vectors, Bioinformatics, Advanced Imaging, and an Animal Facility with extensive capacity to establish the preclinical models. The Center’s technological prowess is matched by unique biological resources, derived from imaging data and biological samples collected from >9,000 participants in CNIC population and clinical studies. These samples are being used to generate genomic, proteomic, metabolomic, and physiological data to integrate biomarker and imaging discoveries to improve CVD diagnosis and prognosis. The center has a strong commitment for large animal experimentation as the immediate

previous step before bringing basic science discoveries into clinical trials. The cutting edge imaging equipment replicated for small animals, large animals and humans help in this translational endeavor.

Identifying and training the best

Excellence in research relies on human potential, and the CNIC is committed to identifying and training the best and brightest talent. Indeed, one of the benefits of bringing basic and clinical researchers together is the opportunity this presents for the exchange of skills through informal and formal training. CNIC training is not restricted to advanced research, but covers all levels under the umbrella of a comprehensive program called the CNIC-JOVEN Training Plan (Figure 3). Training streams within CNIC-JOVEN include long and short courses and are directed both at early-stage researchers and at qualified professionals gaining specialist expertise (eg, physicians receiving training in noninvasive imaging modalities). One of the most successful programs is ACERCATE, aimed at students in their final year of high school, who spend two weeks at the CNIC experiencing life as a biomedical researcher with the aim of awakening their interest in a career in research. CNIC training courses attract more than 500 trainees per year. The CNIC postgraduate training program for medical professionals was recently awarded the *Cátedra de Educación Médica Fundación Lilly-Universidad Complutense* prize. This ambitious Plan is feasible thanks to a solid network of collaborations with national and international research institutions.

Basic research

Basic research is a major pillar of the CNIC's activity. The Vascular Pathophysiology Area focuses on vascular remodeling in atherosclerosis, angiogenesis and aortic aneurysm, intercellular signaling in cardiac development and disease, and the role of inflammation and immune responses in CVD. The research interest of the Myocardial Pathophysiology Area includes studies on mitochondrial genes and the oxidative phosphorylation system, the role of nuclear receptors in lipid metabolism and inflammatory responses, metabolic syndrome and stress kinases, immunobiology of inflammation, inherited cardiomyopathies, cardiac arrhythmias, epigenetic regulation, alternative splicing in cardiac development and heart disease, and protection against myocardial ischemia/reperfusion injury. Finally, the Cell and Developmental Biology Area studies the molecular and cellular embryology of the heart, tissue repair mechanisms, the underpinnings of heart and vascular homeostasis, and how these aspects relate to disease and inflammation, as well as elucidating signaling pathways and molecular principles underlying the mechanical properties, function and adaptability of the cardiovascular system, using state-of-the-art cell biophysics and single-molecule techniques.

Among many landmark studies, some recent representative stories include discoveries of the biology of neutrophil and platelet recruitment during acute injury,¹ the major role of mitochondrial DNA (mtDNA) in ageing,² and the implication of mutations in genes of the NOTCH signaling pathway in inherited cardiomyopathies.³ CNIC researchers recently found that vascular damage during acute injury in different organs is caused by the concerted action between neutrophils and platelets, and only when productive interactions with activated platelets occur do neutrophils undergo secondary activation and pathological inflammation ensues causing irreversible tissue damage.¹ In the field of metabolism, a recent study led by CNIC researchers has shown the key role of mtDNA variants in ageing and diseases.² Through studies with conplastic mice harboring the same nuclear genome but different mtDNA variants, the authors demonstrated that the extensive within-population sequence variability in the mtDNA sequence is not neutral and that mitochondrial and nuclear DNA matching shapes metabolism and healthy ageing. Mitochondrial proteostasis, reactive oxygen species generation, insulin signaling, obesity, and ageing parameters are influenced by the mtDNA haplotype, resulting in profound differences in health longevity between conplastic strains. In the field of cardiac development, work on the role of Notch signaling in ventricular chamber development has revealed a temporal sequence of ligand-receptor interactions regulating trabeculation and compaction which shed light on the etiology of cardiomyopathies and identified novel disease-causing genes.³

The CNIC's achievements in basic research have received worldwide recognition. CNIC groups have published numerous studies in top ranking research journals and the number of CNIC publications with an impact factor >10 has increased 7-fold since 2011 (30 papers in IF>10 journals with CNIC senior author in 2015). CNIC groups have also secured 9 European Research Council (ERC) individual grants in the last few years. These achievements place the Center firmly at the top table and the success in basic research is matched by strong progress in translational and clinical projects, as detailed below.

Clinical Research: translation into treatment and prevention

A major goal at CNIC is to translate acquired knowledge into patient care and public health. The CNIC's emphasis on developing tools for the prediction of preclinical disease represents the surest route to effective prevention. The Center is developing new tools and bioimaging markers for the early diagnosis of CVD that will have a major impact on the way these disorders are diagnosed in asymptomatic individuals. Results from the CNIC's projects will eventually force changes in clinical guidelines in such a way that will recognize atherosclerosis as a lifelong systemic disease with a large asymptomatic "subclinical" phase that should be the main target for diagnosis, prevention and early treatment. In addition to the obvious individual health benefits, the possibility of identifying and implementing prevention at the asymptomatic stages of CVD opens the possibility of

reducing the massive burden on our healthcare systems, since disease prevention is anticipated to be vastly less costly than treating manifest disease.

Progress in this area is achievable through the Center's combination of technological innovation and unique resources, which place the CNIC in a strategic position to run innovative projects in the cardiovascular area. Several key clinical studies, some based on preclinical findings, have already been carried to advanced stages. The CNIC's flagship imaging study is PESA (Progression of Early Subclinical Atherosclerosis, PI Valentin Fuster). Run through partnership with Grupo Santander, PESA is an ambitious study designed to identify new imaging and biological factors associated with the presence and progression of early phases of atherosclerosis.⁴ More than 4000 healthy bank employees aged 40 to 54 years at the time of recruitment have already undergone multiterritory screening for subclinical atherosclerosis by noninvasive 2D/3D ultrasound in the carotids, abdominal aorta and ilio-femoral arteries, together with coronary artery calcium score by computed tomography.⁴ Participants are also assessed for 'traditional' cardiovascular risk factors (including lifestyle and psychosocial factors) and provide blood samples for advanced analyses. A subset of participants with signs of significant plaque burden on ultrasound and CT has undergone multi-vascular imaging assessment by ¹⁸F¹⁸FDG PET/MRI. Subsequent follow-up analyses will shed light on the mechanisms underlying the progression of subclinical atherosclerosis and its early detection impacts the risk of future cardiovascular events.

PESA is linked to the TAN SNIP project (Trans-Atlantic Network to Study Stepwise Non-Invasive Imaging as a Tool for Cardiovascular Prognosis and Prevention), run through partnerships with the Icahn School of Medicine at Mount Sinai, the Framingham Heart Study, and the VU (Free University) Medical Center in Amsterdam. The goal is to develop lifestyle-changing tools based on the results of noninvasive imaging of subclinical atherosclerosis. The outcomes will inform prevention strategies to halt progression of disease before it becomes manifest. This endeavor also studies the relationship between CVD and brain and cognitive function.

These imaging-based prevention studies form part of a spectrum of prevention activities covering 'primordial' prevention, achieved through consciousness raising in young children and their parents and teachers (Programa SI!), primary prevention (PESA, TAN SNIP, the Aragon Workers' Health Study), and the Fifty-Fifty Project, and secondary prevention (the FOCUS and SECURE studies of the CNIC-Ferrer polypill and the METOCARD-CNIC trial in the field of infarct-size reduction in STEMI).

The *Fuster-CNIC-Ferrer* cardiovascular polypill, containing aspirin, ramipril and atorvastatin, is indicated for secondary prevention of cardiovascular events. The successful launch, supported by European funding (Framework Programme 7 and H2020), is testament to the CNIC's commitment to collaborative research, development

and translation. The polypill is currently marketed in 27 countries under two brand names: Trinomia® and Sincronium®.⁵ Polypill-derived royalties will be used to improve transfer and commercialization strategies for the CNIC's other research results.

The METOCARD-CNIC trial is a standout example of the CNIC's commitment to translational medicine that accelerates progress from laboratory to patient. The results of the CNIC-led trial show that treating myocardial infarction patients with the beta-blocker metoprolol during emergency transfer to hospital reduces myocardial injury by as much as 25% as evaluated by MRI and improves ejection fraction at 6-month follow-up.⁶ A definite hard endpoint-powered trial, MOVE ON!, will be initiated soon in several European centers.

Networking and strategic alliances

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 and other research centers. Aware of this, the CNIC has interacted and collaborated with other institutions from the beginning and is currently leading an international large clinical trial (SECURE trial) involving more than 100 institutions from 7 European countries. In the coming years, the CNIC will lead the MOVE ON! and SPHERE trials, recruiting patients with acute myocardial infarction and pulmonary hypertension secondary to left heart disease respectively, testing novel pharmacological therapies based on previous in-house preclinical evidences.

Beyond the coordination of clinical trials, in which hospitals participate by recruiting patients, CNIC seeks active collaboration with national and international hospitals conducting high quality clinical research in the field of cardiovascular research. The Center counts with an ample national network within the Spanish National Health System (65 hospitals and primary health centers) and has currently bilateral programs with several hospitals. . At international level, the CNIC has established partnerships with large hospitals with international prestige in key research areas of interest to the Center.

At national level, the CNIC collaborates with other research centers on a day-to-day basis to develop mainly basic research projects. Most of our partners are based in Madrid and Catalonia.

The Center also provides the organizational basis for efficient translation and facilitates the translation of research results to industry through effective technology transfer. In this area, the CNIC has made significant efforts to develop translational research applicable to the biotechnological, pharmaceutical and biomedical industry. The Center currently counts with 21 active patent families and 16 technology offers available for out-licensing.

Integration of basic and clinical researchers under a joint translational objective: A model for other research institutes to follow?

Dr. Fuster took the leadership of the CNIC in 2006 having in mind as a model the National Heart, Lung and Blood Institute of the USA: the CNIC should stimulate basic discoveries about the cause of disease, enable the translation of basic discoveries into clinical practice, and foster training and mentoring of emerging scientists and physicians.

With that in mind, the CNIC has modernized its organization early in 2015 to further increase multidisciplinary approaches, seeking cross-fertilization between basic and clinical areas to intensify scientific relevance and social return: the 3 Research Areas described above are currently composed by researchers and clinical scientists that work together to tackle large and ambitious translational projects.

Priorities in research are set by CNIC's Operational Committee composed of the General Director, Clinical Research Director, and Basic Research Director in connection with the Managing Director and advised by an international Scientific Advisory Board formed by recognized scientists with expertise covering CNIC's research areas and the Coordinators Advisory Group, composed of the Coordinators of each Research Area.

The main challenge facing the CNIC in the coming years is to maintain the drive and focus established over the past 10 years and to ensure that the Center's basic and clinical scientists continue to work closely together to devise innovative projects that cut across artificial category divides between basic and applied research.

In concrete terms, our advice to other centers is that an institution of this type requires strong international leadership and vision, a stable funding framework to tackle medium and long term projects, a flexible research structure that encourages cross-disciplinary collaborations, access to external support and advice, investment in young scientists and physicians, and the prioritizing of projects with a clear translational component and a focus on societal benefit and economic output. This is the vision and drive that has caught the imagination of all sectors of Spanish society.

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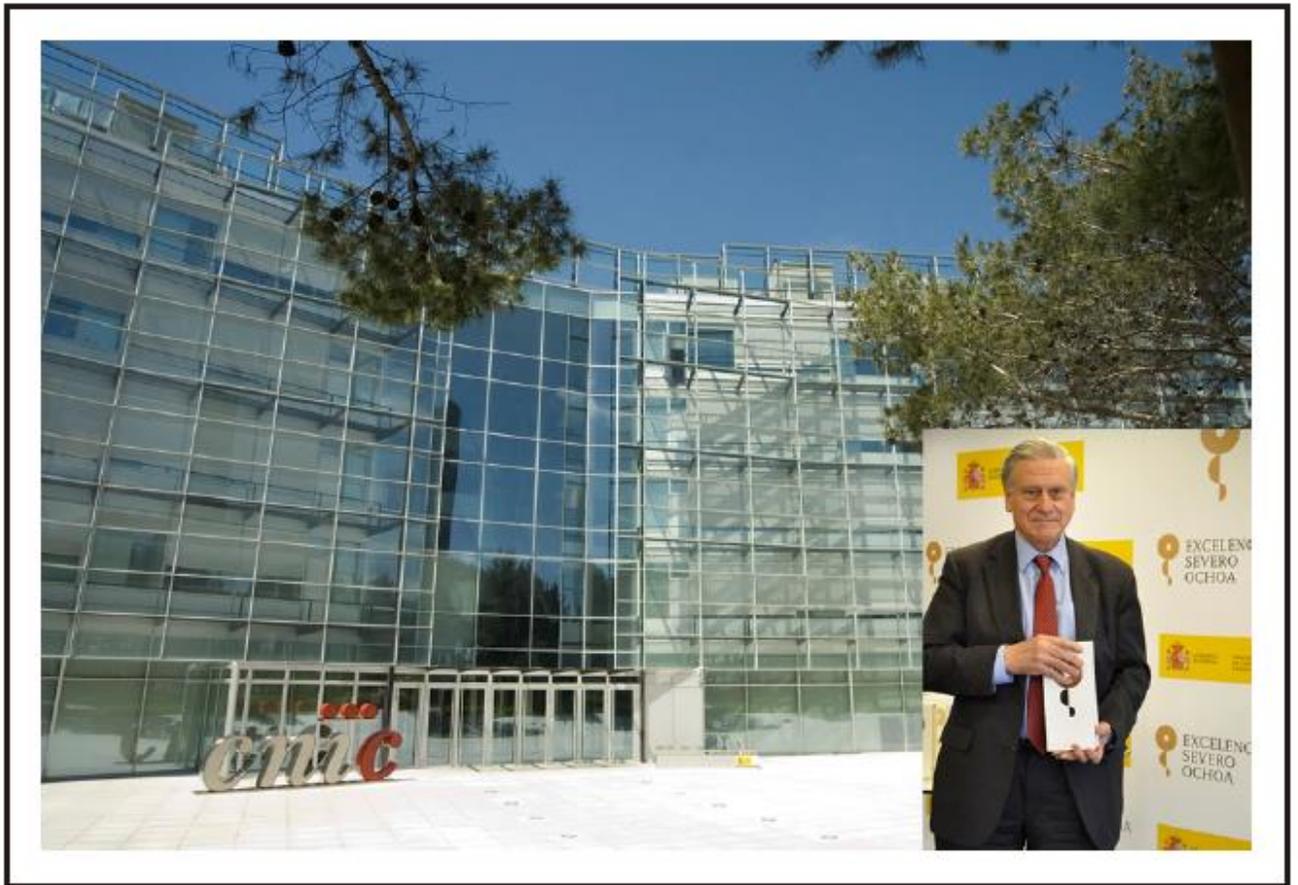


Figure 1. Entrance of the CNIC building. Dr Valentín Fuster receiving the Severo Ochoa Centers of Excellence Program Award. CNIC indicates Centro Nacional de Investigaciones Cardiovasculares Carlos III.

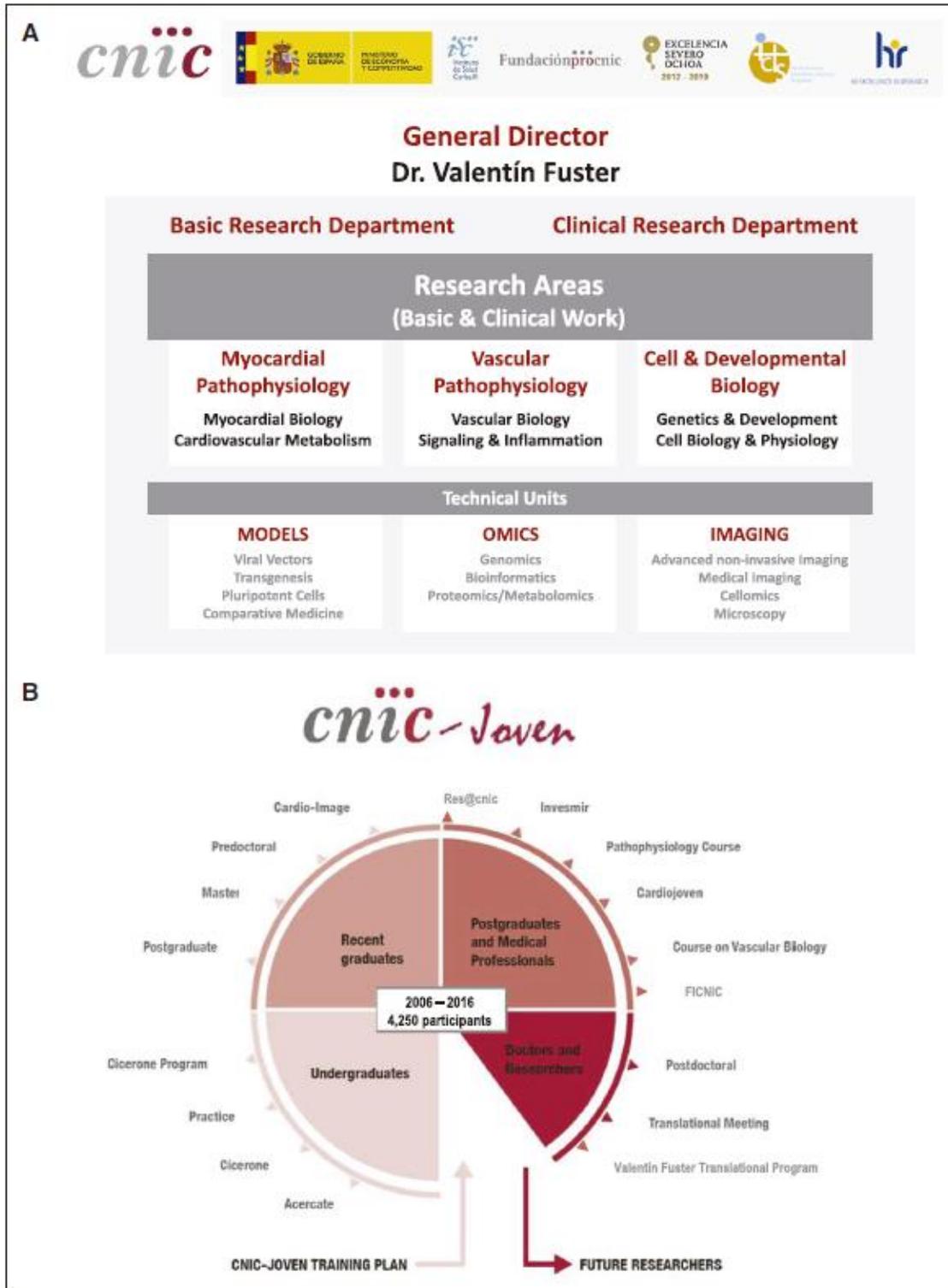


Figure 2. A, CNIC scientific organization. B, The CNIC-JOVEN training program. CNIC indicates Centro Nacional de Investigaciones Cardiovasculares Carlos III.