

TRAIN2GAIN
WHAT'S ON
INSIDE SCIENCE
CNIC & SOCIETY

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CONTRIBUTORS:

Editorial Committee
Jorge Alegre-Cebollada
Vicente Andrés
Héctor Bueno
Borja Ibáñez

Writing
Rafael Ibarra

Content editing
Fátima Lois

Layout and printing
Editorial MIC

Translation into English
TECcientífica

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 Please send any comments or suggestions to flois@cnic.es



“Science is not only making discoveries, but is also engaging society in them”. These are the words of cardiologist and researcher **Dan Roden** of Vanderbilt University, but I have lost count of how many times I have expressed the same idea in one way or another throughout my scientific career. Gone are the days when researchers jealously guarded their findings for themselves and their closest collaborators. In an age when we are permanently connected to the world through innumerable electronic gadgets that are always within our reach, the time has come for science outreach to join scientific research in striving to achieve the accolade of ‘excellence’.

EXCELLENCE IN SCIENCE OUTREACH

And the CNIC, whose maxim is ‘excellence in research’, is also a leader in science outreach. Our researchers are all firmly committed to transferring the results obtained at the CNIC not only to the wider scientific community, but also to the general public. This is reflected in the many scientific articles we published last year in several of the world’s leading scientific journals, including **Nature**, **Science**, **Cell**, **PNAS**, **Nature Genetics**, **JACC**, **Immunity** and **JAMA**. Through this and other activities, the CNIC’s commitment to ‘excellence in outreach’ is helping to inform the public about ‘what’s cooking’ in tax-funded centers and also about the potential societal benefits of research.



CNIC Director **Dr. Valentín Fuster**

In addition, communicating our research findings brings a dual benefit. Not only does it inform society about biomedical advances that are set to impact public health over the medium or long term; it also encourages other scientists to maintain their daily efforts to obtain answers to their research questions. And, indirectly, it serves to foster a scientific vocation among researchers at the start of their careers. These early-stage researchers represent the future of Spanish science, and the

CNIC’s commitment to fostering this vocation is underpinned by our comprehensive CNIC-JOVEN Training Plan.

Prof. Roden expresses it very well in his interview in this latest issue of **CNIC Pulse**. “I try to instill [in young researchers] that their research and discoveries must be disseminated. We must be passionate about our work and know how to convey it”. This is precisely how we see things at the CNIC.

INTERNATIONAL EXPERTS IN THE FIELD OF MECHANOBIOLOGY PARTICIPATE IN THE CNIC CONFERENCE

The CNIC Conferences have become key scientific events for cardiovascular researchers around the world and their success keeps on growing. The sixth edition of the [CNIC Conference](#), held on 4 and 5 November at the National Center for Cardiovascular Research Carlos III (CNIC), was entitled 'Mechanical forces in physiology and disease' and brought together international experts in very different areas of mechanobiology, including technology, cell biology, animal models, human disease, and development. The meeting was organized by four CNIC researchers, [Jorge Alegre-Cebollada](#), [Nadia Mercader](#), [María Montoya](#) and [Miguel Á. del Pozo](#), and by [Martin Schwartz](#) from Yale University.

We live in a gravitational field, and for that reason alone mechanical forces have a profound influence on biology.

Mechanical forces are major determinants of development, physiology and disease of the cardiovascular system. Mechanical forces act on all levels of biology: molecules, cells, tissues, organs and the whole organism. It is known that development of blood vessels and the heart are determined by blood flow, that defects in the contractile machinery induce myocardial remodeling that gives rise to cardiomyopathies, that atherosclerosis is produced in arterial regions subject to blood-flow alterations, and that hypertension and vessel-wall stiffness are the main risk factors for myocardial infarction and stroke.

In fact, mechanical forces are important for many aspects of the structure and function of living organisms. In addition, they play a key role in other diseases, such

**MECHANICAL FORCES
ARE MAJOR DETERMINANTS
OF DEVELOPMENT,
PHYSIOLOGY AND DISEASE
OF THE CARDIOVASCULAR
SYSTEM**





as bone fractures, lung disease, fibrosis and muscle disorders. However, the study of the interaction between mechanical forces and biology has so far been limited by technical difficulties. Fortunately, in the past three decades much progress has been made in this field and the way of understanding biology has changed, and in the next few years models are likely to be found that will make it possible to move from one level of organization to the next. In addition, the information generated by mechanobiology is transforming the way we understand diseases such as cardiovascular disease and cancer.

Among the many eminent speakers at the conference featured Lasker Award winner **Mike Sheetz**, a pioneer in the field and director of the Mechanobiology Institute

in Singapore and professor at Columbia University; **Valerie Weaver**, professor and director at the Center for Bioengineering and Tissue Regeneration and codirector of the Bay Area Center for Physical Sciences and Oncology (UCSF); **Jochen Guck**, researcher at BIOTEC - Biotechnology Center TU Dresden (Germany); and Professor **Julio M. Fernández**, from Columbia University in New York.

The conference was supported by the **Pro-CNIC Foundation**, EMBO, The Company of Biologists, the Spanish Society for Biochemistry and Molecular Biology (SEBBM) and the Spanish Biophysical Society (SBE).

[CNIC Conference: 'Mechanical forces in physiology and disease' \(CNIC, November 4 and 5, 2016\)](#)



PhDAY: THE PhD AND BEYOND



KEY TOPICS OF THIS YEAR'S PhDAY WERE: MAKING A CAREER IN ACADEMIA; WORKING IN INDUSTRY; SCIENCE MANAGEMENT AND TECHNOLOGY TRANSFER; AND SCIENCE OUTREACH

Under the motto "[The PhD and Beyond](#)", the third edition of the [CNIC PhDay](#) was held, an event at a par with any international congress that is slowly but surely strengthening its presence. PhDay is an open forum for undergraduate and graduate students, lab technicians and postdoctoral researchers who intend to develop their careers as scientists, and is based on the exchange of new ideas. This year the congress wanted to give answers to all future researchers who will obtain their doctorate and who are wondering how to proceed with their research career.

The work of predoctoral researchers or of those who, with a doctor's title in their pocket, do not yet have their own research group, is of undeniable importance, but in general they are little talked about. "Many of us already have a doctorate or will obtain it in the near future, but most of us still do not know what to do after that", says **Sarah Francoz** of the PhDay organizing committee. "Obviously we know what to do if we want to work in academia. But there are many other opportunities outside

of academia and we are not aware of how amazing these can be. That is why we must be flexible and open to new challenges and look beyond our horizons. That's why we decided to dedicate this year's PhDay to thinking about our professional development as scientists".

This time, the PhDay addressed four key issues: making a career in academia; working in industry; science management and technology transfer; and science outreach. To try to give answers to those questions, a number of professionals participated who contributed their knowledge on these four issues. The participants were: **Lisardo Boscá** from the IIB "Alberto Sols" (CSIC); **Alejandro Palacios** from Probiotics International Ltd (Protexin); **Fernando Ramón Olayo** from GlaxoSmithKline (GSK); **Fernando Peláez** from the Spanish National Cancer Research Center (CNIO); **Francisco Pérez Vizcaíno** from the UCM; **Javier Peláez**, scientific journalist at Yahoo España, *El Español* and *El País*; **José Miguel Mulet** from the IBMCP (CSIC); **Joaquim Calbó** from the CRG, and **Michael Tadros** from the Botín Foundation.

Like any self-respecting scientific event, the PhDay had its poster section and the two best posters received an award. This year, the winners were "Uncovering the regulation of Arabidopsis ORC1 during root organogenesis" and "Why most of the invited speakers are men".

The CNIC is a research center that has grown very much in recent years and where training is a primary objective. Therefore, the center has a comprehensive Training Plan, called CNIC-Joven, which covers all levels from secondary education up to training of postdocs and young professionals. The plan is designed to bring biomedical

research closer to young people and to create a pool of future researchers of excellence in the cardiovascular area. The PhDay is also a result of this view: in 2014 it was decided to organize an event where young pre- and postdoctoral researchers could meet once a year to exchange results and knowledge, and to create scientific networks.

Last year, a survey was conducted to evaluate the event. In this survey, 90.9% of the participants said that they would like to attend the next PhDay, and almost 85% considered it useful to hold workshops with more interaction between participants.



CNIC-Joven is a comprehensive Training Plan, which covers all levels from secondary education up to training of postdocs and young professionals

THE FUTURE OF OUR COUNTRY'S RESEARCH IS LEARNING AT THE CNIC

THE OBJECTIVE OF THE **ACÉRCATE PROGRAM** IS TO ATTRACT AND TRAIN THE BRIGHTEST YOUNG PEOPLE FROM VERY EARLY AGES ON, TO CREATE A POOL OF RESEARCHERS OF EXCELLENCE IN THE CARDIOVASCULAR FIELD AND TO AWAKEN THEIR INTEREST IN RESEARCH

Elena, Gonzalo, Carla, Mónica, Ana, Alberto, Celia and **Ignacio** were the eight students who participated this year in the 11th edition of the [Acércate Program](#), organized by the National Center for Cardiovascular Research (CNIC). The Acércate Program forms part of the [CNIC-Joven training program](#), and aims to attract and train the brightest young people from very early ages on to create a pool of researchers of excellence in the field of cardiovascular research.

These young people are eight of the best senior high school students in Spain, with a maximum grade average (10) in both years. During the 15 days of the program, **Elena Párraga, Gonzalo Roig, Carla Alonso, Mónica Cacho, Ana Denia, Alberto Alonso, Celia Morales** and **Ignacio Tudela** participated in the daily life of a research center of excellence like the CNIC and could share their experiences and concerns with researchers at the center and with **Dr. Valentín Fuster**, director of the CNIC. **Dr. Fuster** believes that starting training programs at such early stages of education is the key to attracting researchers of the future, because young people are the "future of research in our country".

This is the program that is directed at the recruitment of the youngest talent of all CNIC training programs. The sustained support of the [Pro-CNIC Foundation](#) is indispensable for carrying it out every year, and to continue capturing talent at the earliest stages. "We are very pleased with this concept that we started 11 years ago", adds **Dr. Fuster**. And he concludes: "So, if they feel that 'itch' for doing research, we encourage them to go ahead".

The activities help them to get in touch with research: hands-on experience with among others transgenesis, comparative medicine, proteomics, genomics and bioinformatics, and finally to present the results of their work to their research supervisors.

The 'itch' referred to by **Dr. Fuster** has made itself felt in many of these students. Thus, several participants of previous editions have returned to the CNIC to participate in other programs of the CNIC-Joven Training Plan, specifically the [Cicerone](#) and the [Res@CNIC](#) programs. In fact, according to the CNIC's annual follow-up survey, 70% of the Acércate Program participants remain interested or involved (internships, etc.) in research activities during the course of their university career. These students will be able to return to the CNIC to partake in the next training program when they are in the final two years of their university career. Of those who had the opportunity to participate in one of the other training programs of the CNIC, about 30% have done so and some are currently working on their PhD thesis in our center. Among them is **Claudio Díaz** from the Canary Islands, who participated in this program in 2003 and for whom it was "an unforgettable experience and recommendable for all students, especially if they are interested in science".

And based on what the students said this year, this trend will continue. For example, **Mónica Cacho** has no doubts about her interest in research and science, and it does not come as a surprise that she will study biotechnology. "The fact that you can work in a laboratory and that your findings may serve to treat patients is awesome". From her

experience at the CNIC she singles out the fact of being in touch with the “latest technologies” and she sees herself “working with them” in the near future.

Ana Denia, who has always been interested in science and disease, believes that the program has given her a great opportunity and has opened many doors. And she owes it all to a teacher who told her about the Acércate Program. The young woman from Valencia highlights the relationship with the researchers: “They were always at our disposal. I am delighted at how they answered any questions we had and at how we were treated”. She therefore encourages all students to apply for participation in this program. “It has nothing to do with what you may come across in high school or even at university”.

For her part, **Elena Párraga** from Murcia believes that “it has been a very intense few weeks”, in which she was able to see that, “to reach a certain point, there is an inverted pyramid of work, a lot of effort behind it, which I had not been able to appreciate up to now”. This future medical student especially liked the real possibility of combining “the clinic with research”. “This is where I want to go,” she adds. To encourage other young researchers, she says that “the most important thing is to be passionate about what you do, because it is something that you are

interested in science comes from his family, since his parents are a doctor and a nurse, and although his interests are more directed towards cardiology, oncology and neurology, he does not rule out the possibility that he may change specialty during his studies. He recognizes that the program made him realize that there is an important relationship between the most basic research and clinical practice, and he advises any high school student to participate in programs of this type. For the youngster from Madrid, Acércate contributes among others to “science outreach”, but he believes that it would be helpful if other Spanish research centers developed programs similar to this one of the CNIC, to foster interest in science among citizens.

Celia Morales from Huelva, who was the student with the highest grades for the University Entrance Examinations in all of Andalusia (with a 100% score), opts for the clinic rather than for research, because she is more interested in “dealing with patients”, while **Ignacio Tudela** from Cordoba sees it as a “unique opportunity”, with respect to both the material, “to which many PhD students do not have access”, and the interaction with researchers. He adds that he was surprised by the highly practical nature of the course: “We were allowed to do hands-on work without any problems”.



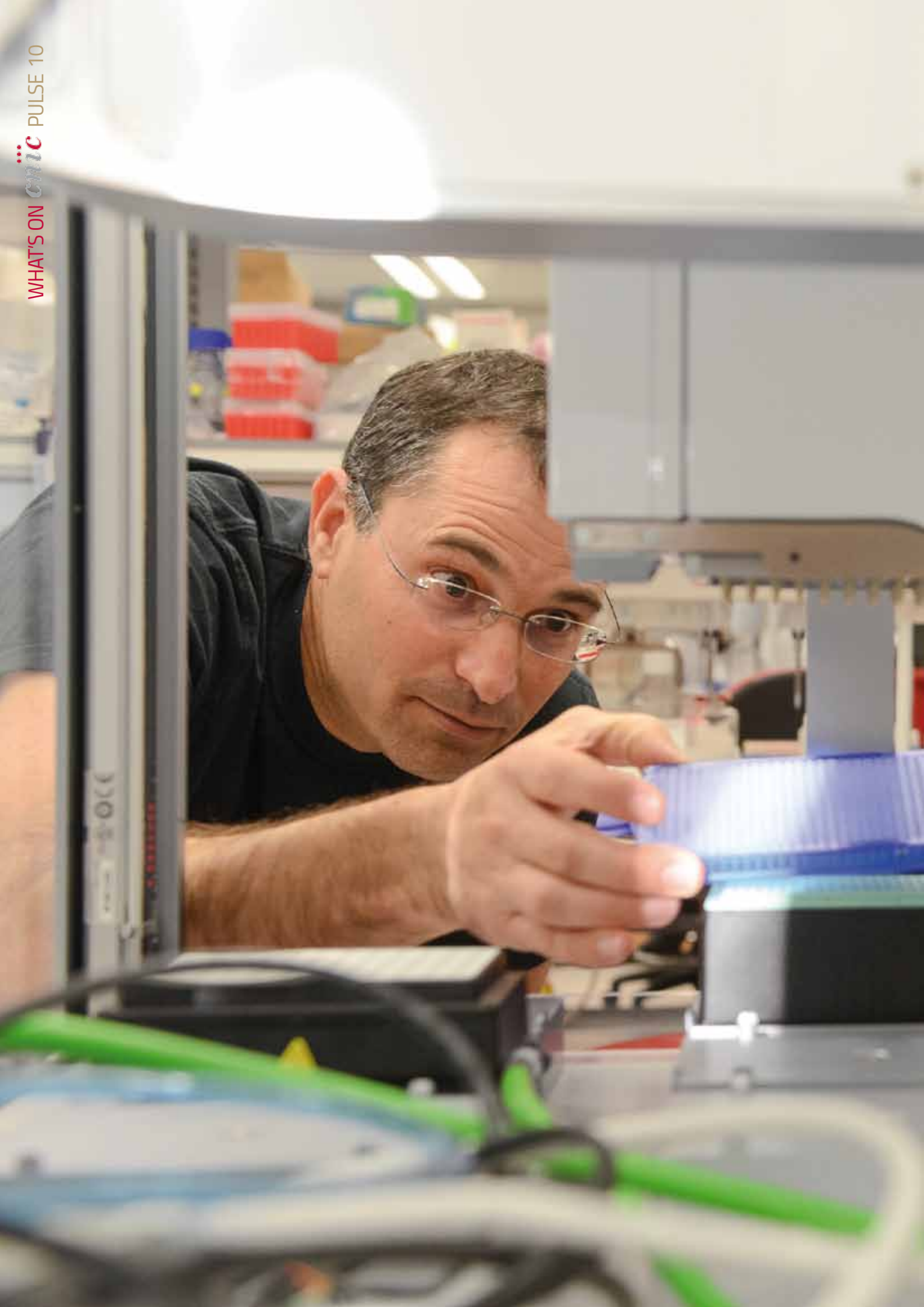
going to dedicate your whole life to. If you don't like it, you are not going to be good at it”. **Gonzalo Roig** expressed himself in the same vein; he discovered, for example, that in science a result that may seem simple needs a lot of work, and that the slightest error means repeating the whole experiment. Based on his experience, this student believes that “without research you cannot advance” and that programs like this one, “where you have access to very sophisticated materials and techniques”, are “an incredible opportunity”.

One of the aspirations of **Carla Alonso** from the Canary Islands is to apply scientific knowledge to improving the quality of life. This future medical student especially appreciated the program, which she described as “incredible”. Thanks to this program, she has rediscovered research. “I love the clinic, but I've seen that without research you cannot make any progress”. **Alberto Alonso's**



Both encourage all interested students “to try to participate in this program”, because “both the facilities and the interactions with the researchers are incredible”. And the Cordoban notes: “Not everyone who likes science has to be a researcher, but it is a field that must be tried out”.

From the point of view of the center, the assessment of the Acércate Program is tremendously positive, especially with regard to three aspects: it is very effective for identifying future research talents, since the results after 10 editions show that the majority of participants will somehow stay involved in research; it promotes scientific vocations by bringing science closer to young people in a practical and realistic way; and it increases the visibility of the center, since it is a pioneering program aimed at very young people. For that matter, the CNIC has set a new and innovative standard with the design and launch of this program for high school students.



Ido Amit

“TO DO ‘GOOD SCIENCE’
YOU MUST BE
CONSTANTLY PREPARED
TO **MAKE MISTAKES**
AND TO **LEARN**
FROM THOSE MISTAKES”

Ido Amit leads a group at the Department of Immunology at the [Weizmann Institute of Science](#) (Israel). While still a graduate student, Amit successfully used systems biology approaches to study cancer in a way that integrated classical biochemistry and a physiological understanding of the way tumors develop. Recently, using single-cell analysis and genomic methods, Amit and colleagues were able to provide a comprehensive model of chromatin dynamics during blood development. Using hematopoiesis as a model to study chromatin state dynamics, Amit's team identified approximately 50,000 hematopoietic enhancer regions and characterized their dynamics. Their work allowed them to uncover the regulatory regions utilized in blood cell development and set the grounds to identify regulatory regions involved in many diseases by applying similar approaches in human cohorts. Among others, Amit has received the Ernest and Bonnie Beutler Research Program of Excellence in Genomic Medicine and the 2015 EMBO Gold Medal.



“As our knowledge is growing, immunotherapy is going to have an increasing impact on the treatment of many tumors, and not of just a few as is currently the case”

In 2015 you received the [EMBO GOLD Medal](#) for your research into the workings of the immune system and your contributions to improving health. From a purely medical point of view, how can knowing how the immune system works be applied to health?

In recent years we have advanced in our knowledge of how the genome and the immune system affect different physiological events, such as for example cardiovascular disease. In our specific case, we are investigating how the immune system modifies specific sequences of our genome. And unlike studies comparing groups of individuals with different diseases, we propose a different approach based on the function of the genome and its regulatory mechanisms.

You were one of the first to employ a systems biology approach to study cancer in a way that integrates classical biochemistry and physiological knowledge, and your recent work focuses on how gene regulatory systems and chromatin control the formation of the cellular components of the blood (hematopoiesis) and the immune system. At what stage are your studies?

My father was an engineer and thanks to him I came to understand the importance of complex systems, such as electrical circuits. I believe that applying this knowledge to research into biological systems can give us a much more realistic picture of what happens, for example, in the functioning of the immune system, but also to solve biological problems. That's what I tried to do with my research: apply these engineering concepts to biology and genomics. And I believe that these approaches to biology and genomics are beginning to have a major impact on various areas of immunology. For example, we recently published a study in which, through the use of a multidisciplinary and integrated approach of biochemistry, computer science and physics we were able to learn more about different regulatory mechanisms of the immune system, which may serve, for example, to design better treatments for some diseases of the brain. Over time, we

will progressively see the benefits of this multidisciplinary integrated approach in the design of more personalized drugs for patients.

Your research is characteristic of a new breed of biologists who apply new technologies to the knowledge of the post-genomic era. To what extent do these new technologies contribute to your research?

In many ways; for example, to learn the bases of biological problems and their changes in certain diseases that affect specific cell types. Thus, we were able to gain more insight into the mechanisms of hematopoiesis, as recently published in [Cell](#), thanks to high-resolution technologies that can distinguish between the different cell types of the immune system or the blood. I think it is the beginning of a new scenario that will allow us to make advance not only in knowledge, but also in new treatments for cancer or diseases of the immune system once we know with much more precision which cells are altered. But above all it will give us a much more detailed, and at the same time more global, view of the immune system and its functioning, which goes far beyond our current knowledge.

During your visit to the CNIC you talked about your research on the immune system in a seminar entitled 'Shaping the blood: lessons from Chromatin and single cell RNA-seq dynamics'. What exactly did you refer to?

I wanted to address different areas and the way we are working to investigate the different cell types of the immune system to identify new signaling pathways involving genes that are important for different phenotypes. I also explained some aspects of chromatin regulation, how it is affected by changes in the environment and how it works during developmental processes.

In recent years there has been much talk about the immune system for the treatment of different diseases, such as cancer. What will be the real impact of immunotherapy on human health?

"The biggest goal in science is progress. And to reach that goal we must take risks: we cannot make progress in research if we stay in our comfort or safety zone"

I think that immunotherapy is a very interesting tool for the treatment of cancer, especially because it synergizes with other treatments that target the tumor itself. As our knowledge is growing, immunotherapy is going to have an increasing impact on the treatment of many tumors, and not of just a few as is currently the case. In addition, one of the most interesting aspects is that it will have a great impact on other diseases as well, not just on cancer. It is really just the 'most natural' way to tackle diseases and it is likely to have the least number of side effects. But we will see all this in the next few years. We are just at the tip of the iceberg.

What is your impression of the CNIC? Do you think there is any possibility of collaboration?

There are some Spanish researchers in my center who told me about the CNIC and the research of excellence that is being done here, but this is the first time that I am visiting it. And I'm very impressed. I have seen some areas where we can synergize, especially areas related to the cardiovascular system in which the CNIC is a leader. Collaborations between centers often depend on 'a good feeling' between two researchers and I hope this will be consolidated in the future.

You lead a group of more than 20 people. In your opinion, what qualities should a researcher have?

I always tell my students that you must take risks in science all the time. If you address the same things others are investigating, your research will not take you anywhere. The biggest goal in science is progress. And to reach that goal we must take risks: we cannot make progress in research if we stay in our comfort or safety zone. But the truth is that, as in life, researchers feel safer in their comfort zone. And to do 'good science' you must be constantly prepared to make mistakes and to learn from those mistakes. That's the way and that's what I tell my students.



[Seminar: 'Shaping the blood: lessons from chromatin and single cell RNA-seq dynamics' \(January 2016\)](#)

Invited by Miguel Torres & Mercedes Ricote



VANDERBILT UNIVERSITY (UNITED STATES)

Dan Roden

“SCIENCE IS NOT ONLY
MAKING DISCOVERIES,
BUT ALSO ENGAGING
SOCIETY IN THEM”

For the past 10 years, Dr. Dan Roden has been directing research at [Vanderbilt University](#) (United States) focused on pharmacogenomics. He is at that university the principal investigator of the National Institutes of Health’s Pharmacogenomics Research Network (PGRN) and of the National Human Genome Research Institute’s Electronic Medical Records and Genomics (eMERGE) Network. In addition, he directs the Vanderbilt DNA databank BioVU, which includes more than 175,000 samples linked to their electronic medical records. He also heads the PREDICT Project, which since 2010 has prospectively incorporated pharmacogenomic data into the electronic medical records of more than 14,000 patients. Among other awards, Dr. Roden has received the Goldberg Young Investigator Award and the Rawls Palmer Progress in Science Award from the American Society for Clinical Pharmacology and Therapeutics; the Distinguished Scientist Award and the Douglas Zipes lectureship of the Heart Rhythm Society; and the Distinguished Scientist Award and the Functional Genomics and Translational Biology Medal of Honor from the American Heart Association. He is currently a member of the Science Board to the US Food and Drug Administration and has been elected a member of the American Society for Clinical Investigation and of the Association of American Physicians.

The journal *Circulation Research* elected you as one of the 'new leaders in Cardiovascular Science'. What does that mean for your career?

I'm not sure why they said that. What I can say is that throughout my career I have tried to ask interesting questions and to find answers that I believe are also important. I tried to answer those questions with any technique available at that particular moment. I am a clinical pharmacologist and as such I am very interested in the bioavailability of drugs. But I also am an electrophysiologist, and for that reason I have been investigating for years the mechanisms underlying arrhythmias and the response to treatments. In addition, in recent years I started working on molecular genetics and on how to apply genetic information to population groups. Somehow I have different careers. I feel fortunate to work in a place that supported my career and that provided me with the resources to answer all the questions I asked myself. In addition, we developed many collaboration projects with other national and international institutions to find answers to the questions we raised. I am grateful that *Circulation Research* named me one of the new leaders in Cardiovascular Research, but the reality is that I am very fortunate to be able to carry out my research with all possible support.

What do the results in genomic research mean for human health?

Many of our traits are transmitted through genes: familial diseases, some of which are rare and others more common. And we have learned a lot about the genetic bases of diseases such as cystic fibrosis and even primary atherosclerosis. Genetic information has been extremely useful for us to pay more attention to those families, but it has also been very important to advance our understanding of the mechanisms involved in these and other diseases, because we have been able to identify new biomarkers that lead to new drugs. Not only for the families affected by these diseases, but also for the general population. The question is how we can use this genetic variability that we know exists in individuals, and therefore in the population, to advance our understanding of the mechanisms involved in diseases, to predict their progression or to develop biomarkers, drugs, etc. I think there is a space in genomics for population studies. We may think that genome-wide association studies have failed to find, for example, the gene for diabetes or atherosclerosis. But in fact these studies are very valuable because they allowed us to progress in our understanding of susceptibility to diseases in a way that until now was unthinkable. The way is to combine genomic studies of families with genomic population studies, which together make up what we call the 'genetic architecture of common diseases'. And that is likely to have an impact on the health of the population. But in addition, population studies, which include many people, provide very interesting information from the point of view of drug response. If large populations are analyzed, you will find individuals who have very unusual responses to drugs. And so we can identify those patients in whom the drugs can have catastrophic consequences. Moreover, genetics serves

to identify people who will respond well to treatments, or, for example, to investigate cases of individuals who should be ill and yet are not. Somehow they are protected and it is our job to identify them by genetic studies in large populations.

In your opinion, what have been the greatest advances in pharmacogenomics?

Everybody knows that a drug does not have the same effects in all individuals. Much of this variability in response to treatment may be related to external factors (poor compliance, etc.), but there is always a genetic component. Genetic variability can cause a drug to have serious adverse effects in a person. And that is where pharmacogenomics comes in: the idea that genetic variations determine a better or worse response to treatments. Our hopes are to identify the genetic variations that tell us with 100% certainty if an individual will respond well or poorly to a given drug or if it will have very serious adverse effects. Many people think that we are totally determined by our genes and that if we identify them we will know our response to treatments. But the reality is that the currently available genetic markers only give us information in terms of probabilities, they do not give certainties. We cannot know with complete certainty if an individual is going to respond to a treatment, but we do know which people are more likely to respond to therapy.

What do you expect will happen in this research field in the coming 5 to 10 years?

In the coming years we will see progress in two very specific areas. On the one hand we will have more and more genetic biomarkers that can predict a response, good or bad, with much greater certainty than today. And in addition, the greatest opportunity in pharmacogenomics is to use the advances that are being made in basic research on the mechanisms underlying diseases to design new drugs that are much more effective, specific and better tolerated. It will also allow for a better selection of candidate patients.

You head the PREDICT project at Vanderbilt University. What are your goals?

My job is twofold: on the one hand I have to take care of patients and on the other I have been studying the significance of genetic variability for many years. As a research scientist I know that genetic markers may help predict which patients will respond to treatments. But on the other hand, as a clinician I also know that doing routine genetic tests is an impractical idea for most drugs. The best example we find in psychiatry: there are more than 20 different genes linked to depression. For what gene or genes should we do the genetic test? Furthermore, the results do not say "yes" or "no", but rather if there is more or less probability of responding to a drug. The initial inspiration for PREDICT came about when we started using electronic medical records of our patients in the year 2000. That's when we began to see more clearly that it would be useful to do genetic testing of individuals and to put the information into their medical



records. This way, when someone prescribes a drug he or she can see in the medical record what the response to a particular drug would be, based on the patient's genetic results that are already available to all doctors. And this facilitates the work of the clinician, who does not have to remember or request it: it is all available in the medical record. This is the pharmacogenetics that can help us in clinical practice. In addition, as genetic testing is done on more individuals, we will have more information on responses to treatments. We are getting closer and closer to predictive medicine.

From the beginning of your career you focused on research on arrhythmias. Why?

One of the most interesting questions you can ask a researcher is why he or she has focused on a particular area. In my case I can say that I found arrhythmias fascinating; they are like a detective story in which through an electrocardiogram you can see how electricity is generated through the heart with only a few small clues. Sometimes you can look at an electrocardiogram and tell if a person has a mutation in a particular gene: there is no other example like it in medicine, except cancer. It's fascinating! My career would probably have been different if I had focused on another disease, but who knows?

What do you tell young researchers about the future of science and medicine?

We are living one of the most exciting moments for science. The tools we have today are incredible and allow us, for example, to make cardiac maps with a

level of detail that was unthinkable 20 or 30 years ago, when I started to do research. We can ask ourselves fundamental questions and now we are able to answer them! We can edit the genome thanks to technology! These are fascinating times! The opportunities for the researcher, and for the results to reach the clinic in a very short time, are unimaginable. We have never been in a similar situation in science before. And that's what I tell my researchers. But I also tell them that you must know to ask the right questions to find answers that have a real benefit for the patient. And also, which is not less important, that we must enjoy everything we do, although sometimes we do not have the tools, as we did 20 years ago. If your career makes you suffer, you better do something else. I also try to instill in them that their research and discoveries must be disseminated. Science is not only making discoveries, but also making society participate in them. We must be passionate about our work and know how to convey it. And finally, another thing I emphasize to young researchers is that they must not let themselves be seduced by technology. We can sequence a genome, make a map of a myocardial infarction ... but what has to captivate us are our questions and, once we have raised them, to know the best way and the best tools to answer them.

[Seminar: 'Adventures in understanding and managing variable drug actions: from QT prolongation to population genomics' \(February 2016\)](#)

Invited by Miguel Manzanares

RIKEN CENTER FOR DEVELOPMENTAL BIOLOGY (JAPAN)

Hiroshi Hamada

"A SCIENTIFIC
CAREER
IS ALWAYS
DIFFICULT"

Hiroshi Hamada is director of the [RIKEN Center for Developmental Biology in Kobe](#) and Professor of Developmental Genetics at the Graduate School of Frontier Biosciences, Osaka University (Japan). Dr. Hamada received his M.D. from the Medical School of the University of Okayama in 1975, and after 5 years as a postdoc at the National Institutes of Health (NIH) he became an assistant professor at Memorial University in Newfoundland (Canada). Prof. Hiroshi Hamada is considered one of the most prominent scientists in Asia and his discovery of the Lefty gene, which determines the differences between the left and right side in living beings, earned him the [Keio Medical Science Prize](#) in 2014. From his laboratory at the Riken Center, one of the most renowned research centers in Regenerative Medicine and Developmental Biology, Hamada works to gain a better understanding of the fundamental processes of animal development in the field of molecular and cellular biology, the most complex phenomena involved in organogenesis, as well as stem cell biology and tissue regeneration. This research will be fundamental to improve the effectiveness of regenerative medicine for the benefit of society. The professor participated in a seminar at the CNIC, where he gave a presentation entitled "The origin of asymmetries in the mouse embryo".





Could you briefly explain your current research?

My laboratory has been studying for a long time how animals develop asymmetry. We know that our body is asymmetrical. We have been studying especially left-right asymmetries; these asymmetries are established at a very early stage of embryogenesis. So, we want to know how and when symmetry is broken. Until we reach those stages, everything is symmetrical, but for reasons still unknown that symmetry is broken and we do not know how. Asymmetry is necessary; otherwise we would not have a head or feet. There must be a system that determines which part is, in the end, a head or any other organ; otherwise our body would be like a ball.

What do you find most fascinating about your research?

For researchers, the moment in which for example an unexpected and unknown mechanism is identified for the first time is always exciting. My research analyzes the emergence of asymmetries. Until a certain stage of development there is no difference between left and right in the embryo. But then asymmetries arise and that is something really surprising, unexpected. The mechanism involves structures called cilia. And, although the existence of these structures was known, their role in the establishment of asymmetry was unknown. Somehow, rotation of the cilia leads to breaking the left-right symmetry: rotating cilia generate a leftward fluid flow, and immotile cilia detect this fluid flow.

Do you remember why you chose to be a researcher?

I think I decided to do science when I was very young. I must have been about 10 or 12 years old when I decided to be a doctor, but I also knew I wanted to do basic science. I never thought that choice would be difficult for me. But a career in research is always difficult. To become an independent researcher you must show proactivity, but also have good ideas, etc. As a researcher you must have, we all must have, many abilities, but while experience can be acquired, curiosity and good ideas cannot. I am certainly very proud to have opted for a scientific career.

What is a typical researcher's day like?

In my case I have to admit that I am currently doing more administrative work than anything else, although I still have my laboratory. I used to spend 80-90% of my time doing my own research, planning and doing experiments myself.

Do you recall the most memorable moment of your research career?

There have been many memorable moments in my career. It is very difficult for me to select only one, but I remember that 20 years ago I changed the course of my experiments. I was working on how embryonic stem cells maintained pluripotency. But something happened that made me switch to embryology; I was looking for a gene that is only expressed in pluripotent cells and I obtained a lot of information. But looking at expression in the embryo, not in cells, I found a gene that showed an



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“The big question is what you would like to do in your scientific career, what you would like to know”

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“My center in Japan is similar to the CNIC; we also do basic and translational science. I think this strategy is important because it allows basic scientists and clinicians to communicate and to stimulate each other”

asymmetric expression. In other words, this particular gene was expressed only on one side of the embryo, the left side. That discovery led me to start investigating asymmetries. We called the gene Lefty because it is expressed on the left side of the developing embryo.

What advice would you give to young scientists who are at the beginning of their scientific career?

Young researchers should study hard, read a lot of articles, etc. For example, when I was a young graduate student I used to read a lot of articles and think about what really interested me. That is what I would recommend to young students. But the big question is what they would like to do in their scientific career, what they would like to know.

What, in your opinion, is the most important quality a scientist should have?

I cannot mention just one; researchers need different qualities to achieve success in their scientific careers. The first is to have good ideas, but you must also know the best way to design your experiments and how to analyze them. And of course, you must publish your studies. Until that point everything seems interesting, but you must know how to analyze and summarize the results, and then draw some conclusions. Some people are good in one or two areas: they have good ideas, for example, but they cannot publish, or they know how to publish but they do not have good ideas. And another important issue, which we often forget, is communication. As your

career develops, communication will become increasingly important. You cannot do science on your own; you need collaborators. I know many people, especially young and important researchers, who are poor at communicating even though they have very good ideas.

What is your impression of the research being done at the CNIC?

It is a very good idea to have basic and clinical science in one place. As far as I know, there are not many institutes in the world that do this. My center in Japan is similar to the CNIC; we also do basic and translational science. I think this strategy is important because it allows basic scientists and clinicians to communicate and to stimulate each other. And that is very important.

Who had the most important personal influence on your career, and why?

I had two important mentors during my career. The first was my supervisor in graduate school; he was very open-minded and taught me the importance of focusing on the 'big question'. Later, when I was a postdoc in Boston (USA), my supervisor showed me how much you have to do to become an independent researcher, because not everything is science.

[Seminar: 'The origin of asymmetries in the mouse embryo' \(June 2016\)](#)

Invited by Miguel Torres

“One of the most fascinating discoveries was the concept of cellular reprogramming, especially reprogramming induced by a only few genes”



Isabel Fariñas

“RESEARCHERS MUST
NEVER
LET THEMSELVES BE
DISCOURAGED”

Dr. Isabel Fariñas directs the [Molecular Neurobiology Unit of the University of Valencia](#), where the regulation of adult brain stem cells and their possible therapeutic potential is investigated. Her group forms part of the ERIC/ISIC of Biotechnology and Biomedicine of the University of Valencia, the Spanish National Cell Therapy Network (RETIC TerCel), and the [Biomedical Research Networking Center on Neurodegenerative Diseases \(CIBERNED\)](#). Dr. Fariñas knows that “it is possible” to do research of excellence in Spain, despite the fact that at the present time circumstances are not optimal. However, as she herself acknowledges, researchers must “never let themselves be discouraged”. She recently gave a seminar at the CNIC entitled ‘Sitting on the dock of the bay: Vascular influences in neural stem cells’.

In what area are you currently working?

We are trying to understand how adult stem cells behave and, therefore, how they can be modulated, specifically those located in the adult brain. We do this with a very simple concept used by other laboratories working in the field of adult stem cells: since they always seem to be in specific microenvironments, we want to understand what kind of environment is conducive to their maintenance and functioning. If we understand these processes, in the long term we could move forward, for example, to improving the condition of our tissues and organs acting on them, perhaps at the pharmacological level, but to do that we

need to have a much better understanding of how they work. This information could also help us to understand the impact on aging at the time these cells lose their potential during their lifetime and, as a result, know how to mitigate these effects.

What is your view of the present and future of cell therapy?

Cell therapy is a very attractive field that can offer solutions in the near or more distant future, depending on the tissue. People have been working on cell therapy for more than 30 years in the hematologic system; that is a reality. It is also a reality that today corneas or skin are being generated in

vitro, and we know that much progress has been made in osteoarticular repair by mixing biocompatible materials that act as scaffolds for cells. In Spain, much work has been done on adult mesenchymal cells and wound healing. But when it comes to organs such as the heart or the brain we are talking longer term. For example, if we refer to a neurodegenerative disease, such as Alzheimer's, we must keep in mind that it is a diffuse neurodegenerative pathology in which many neurons die in different areas of the brain, and these neurons are also interconnected with thousands of other neurons. Because regenerative medicine today is based on cell transplantation, it is a bit bold to think that it is feasible today. And that is why we have to do much more research into the properties of these cells, into finding the right source and how to do it. That is why, even though it seems 'something of the future' to understand how our stem cells work, this information may give us some clues on how to proceed without having to resort to transplants. And if we are speaking specifically of the Central Nervous System (CNS), a transplantation approach is difficult to imagine as a viable solution in diffuse neurodegeneration, although it has been shown to work for some diseases such as Parkinson's in which a more specific area is affected. It has been observed that when cells were introduced into the brain, no neurons are generated that integrate into the circuits. Rather, they seem to play a trophic role: they release substances, molecules that favor the remaining neurons to connect better and take longer to die. But to think that we can activate our own stem cells is a bit foolhardy, considering that in the brain there are only two locations where stem cells are

produced naturally. What is being investigated is that these stem cells belong to the astrocytic lineage, and it is already known that there is a proportion of astrocytes, located in a juxtavascular position, that are able to return to a neural stem cell state, and this way they become neurogenic. This has been shown to occur in response to e.g. ischemic and mechanical CNS injuries. And we think that if some of these astrocytes, located throughout the brain, could be induced to go back to an earlier, more primitive state and give rise to neurons, we could generate neurons in any part of the brain. But this is still very far in the future and will require a thorough knowledge of the signals and mechanisms that regulate the behavior of stem cells, as well as of the possible behavior of astrocytes that have been converted to a neurogenic state. That would be fantastic, but we still need to do a lot more research.

What, in your opinion, has been the greatest scientific finding in your field?

For a cell biologist, one of the most fascinating discoveries was the concept of cellular reprogramming, especially reprogramming induced by only a few genes. It has revolutionized the way we think in the fields of cell biology and development. It has completely upset the way we understand cells. We are currently in the middle of a cellular revolution.

What made you go into research?

I knew I wanted to be a scientist since I was a child. When I was 13, all I wanted to do was biology, and I wanted to do research in biology. It was entirely vocational. But I cannot



say why, it's as if I have always known. I was fortunate that in my family no one questioned what I wanted to do.

How is the day-to-day life of a researcher?

I am a clear example of a researcher at a Spanish university. I am referring to the fact that we have to reconcile our research with our teaching load, which is no small thing. On the one hand you contribute to teaching new generations, but on the other hand you have the disadvantage that it is difficult to find a critical mass to devote to a given subject, like there may be in the CNIC, which is something to be jealous of.

What qualities do you think a scientist must have?

A scientist has to have creativity, talent, etc., but if there is one thing that defines us it is a notion of almost humility. Researchers must never let themselves be discouraged. There are many hardships. You cannot invent things, creative as they may be; you have to bow down to the problem you are facing. Many times what you get on this journey is a lot of frustration until you start to see things more clearly. That is why you must never let yourself be discouraged, something you can only do if you really enjoy what you are doing.

Would you like to share with us something funny that happened to you?

I remember when I was postdoc in Barcelona I was doing an experiment that just wouldn't work. After a week of failures, I tried again on a Saturday. At 20:00, after yet another failure, and making my friends wait with whom I was going to have dinner, I left without cleaning up anything. I am a methodical and considerate person, and when I work in common areas like a laboratory I always clean everything up. But that day I was so frustrated that I did not clean up anything: I took the container, put it in the cold room, and left. And you know what happened? Monday I had the result: I only had to give it more time. That may be a good story for beginning researchers.

Who has been the most influential person throughout your career?

I have been influenced by many people. This is a job in which you are always indebted to your mentors and only pay back to younger people. Perhaps the person who taught me most was **Louis F. Reichardt**, my boss and researcher at the [Howard Hughes Medical Institute at the Department of Physiology, University of California, San Francisco, USA](#). He had an extensive knowledge of biology; he worked on one subject but had knowledge about any subject in biology. That 'erudite' view of science was almost spectacular. What amazed me most was his almost obsessive curiosity to 'take in' everything that was being investigated. His laboratory had researchers who had done their theses on the most varied subjects. He did not have researchers specialized in the subject of his laboratory. It was a kind of melting pot. And that can only be done by a personality who likes science in a broad sense. **Lou Reichardt** is also an American hero, as he was part of the first expedition to the East Face of Mount Everest (the Kangshung Glacier) and scaled the K2. To him, each

had his or her own scientific Everest and he gave complete freedom. But, of course, it was difficult to enter his office and say that you had failed in a simple experiment.

What advice can you give to researchers who are just starting out?

I always tell them that it is possible; otherwise I would not be able to teach. I have colleagues who say 'why? if we are going to train them to go abroad ...' It is not only the best-trained generation, but all of us have paid for it. And society does not know that, and they have to be told. The problem is not that they are leaving, because they will be treated very well; the problem is for those of us who stay. Going to work abroad is very good for a researcher; but these days they do not return, we cannot bring them back. And we do not realize that if we do not recover that potential, we will not advance.

How do you think the crisis has affected Spanish science in that sense?

It is not something new. Spain chose to be "rich rather than educated". I mean, before having a society educated in technology and appreciation for science and progress, money from Europe started raining on us, and we probably did not realize that this was a great opportunity to promote progress and education in our country. Our politicians do not invest in science because society does not truly feel that it is useful, that is the great tragedy. If society were aware, it would force politicians to invest in science. When asked how science can be improved in Spain, I say that we will not improve until we start investing in primary education. But that is obviously also a matter of making investments; we are no less smart than any other country, there are very good people and we do not lack 'brains'. Science is done by scientists, but they lack means. In recent years, with the creation of centers like this one, a critical mass was being generated that was changing the scientific landscape of our country. But that has stopped! And we did point out that the scientific community in our country was being depleted. For a few years it was possible to recover scientists, many of them Spanish, who were working in other countries. And that meant an increase of the critical mass in Spain. But that has been nipped in the bud; the critical mass, which is what promotes excellence in research, is no longer being increased.

What is your opinion on the research carried out at the CNIC?

These types of center are not just a spectacular idea; they are beacons that remind us of what can be done if people use their heads and have the right investment, and believe in researchers. It helps me to stay optimistic. The first time I walked into one of those centers, I thought, "yes, it is possible," "this country can do it". It shows that if you have sufficient investments and if you really want it, it can be done. By all means, they serve as a standard in my research work.

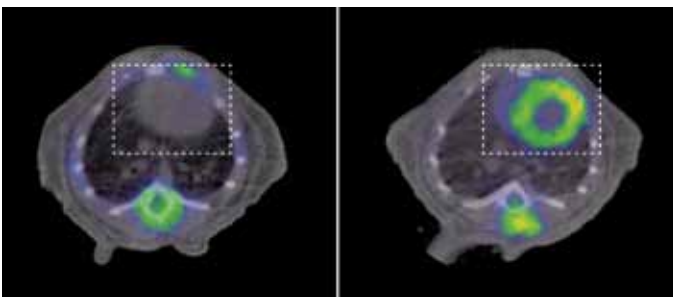
[Seminar: 'Sitting on the dock of the bay: Vascular influences in neural stem cells' \(May 2016\)](#)

Invited by Miguel Torres

EXCELLENCE IN SCIENCE OUTREACH

THE **MOST IMPORTANT SCIENTIFIC JOURNALS** ARE PUBLISHING RESEARCH DONE IN THE LABORATORIES OF THE CNIC

Science, Immunity, Nature, Cancer Discovery, Circulation Research, Cell Metabolism, The EMBO Journal and *JACC* are a few of the scientific journals that have published research conducted in the CNIC; some of these studies were even invited to provide the cover of these journals with an impact factor of more than 10. We present a selection of high-impact studies published in recent months.



SCIENCE

Science published a study carried out at the CNIC by [Jaime García-Prieto](#) and [Dr. Borja Ibáñez](#), in collaboration with the CECAD Research Center of the University of Cologne/Max Planck Institute (Germany) and with the participation of the University Hospital Fundación Jiménez Díaz and the CEU of Madrid, which identified a defect in a mitochondrial process vital for heart cells as causative of a type of dilated cardiomyopathy, a heart disease that in humans leads in most cases to heart failure and premature death. The study uncovered the key role of the protein YME1 in regulating the



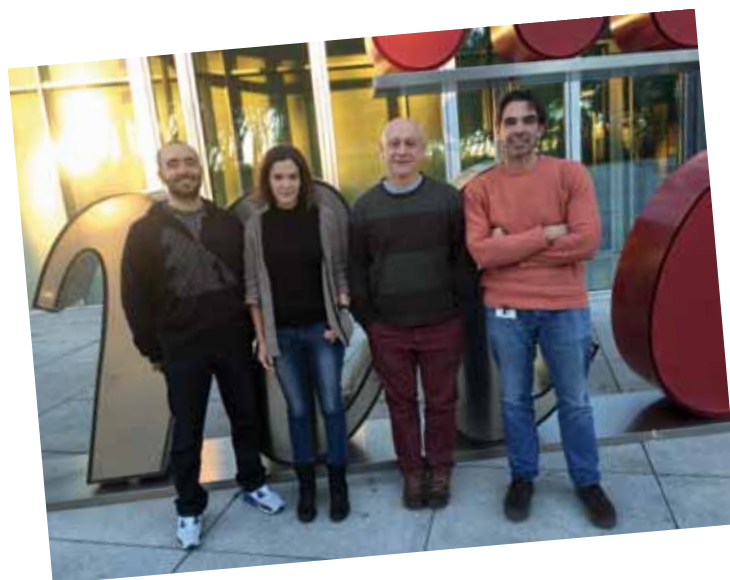
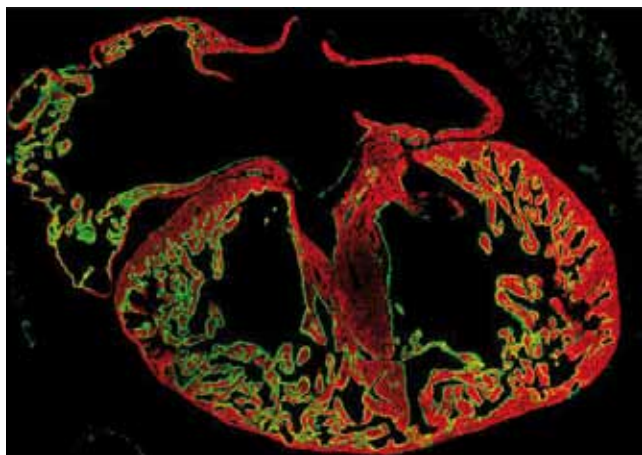
number, type and shape of the mitochondria, and how its absence results in a type of deleterious metabolism typical of patients with heart failure. The study also showed that using metabolic strategies was sufficient to restore the correct functioning of the heart, which opens the possibility to treat patients with this disease in the future, although, as the authors warn, this is an experimental approach to a high-fat diet as a therapeutic measure in a model of dilated cardiomyopathy.

NATURE CELL BIOLOGY

The prestigious journal *Nature Cell Biology* published the results of a study led by [Dr. José Luis de la Pompa](#), which found that the NOTCH signaling pathway plays an essential role in ventricular development, and which also identified new candidate genes that are potentially involved in severe inherited cardiomyopathies (non-compaction left ventricular cardiomyopathy and dilated cardiomyopathy). The finding may have important clinical implications for the diagnosis and classification of patients with hereditary cardiomyopathies.

The ventricular chambers are essential for contraction and relaxation of the heart; however, when there are congenital defects in the ventricles, one of the consequences is the development of hereditary cardiomyopathies. The problem is that until now there was little information on the mechanisms involved in the formation and development of ventricular chambers. But in this study the mechanisms that regulate activation of NOTCH at different moments of development of the ventricular chambers were identified. The authors observed that during ventricular development the presence of sugars on the extracellular domain of the NOTCH1 receptor, a result of the activity of the MANIC FRINGE (MFng) protein, determines if this receptor is activated by one ligand or another. In early ventricles, the researchers explain, structures called trabeculae arise. "The purpose of trabeculae is to increase the surface area of cardiomyocytes for exchanging oxygen that is brought by oxygenated blood with every heartbeat", says [Dr. de la Pompa](#). And during the formation of the trabeculae, the MFng protein adds sugars to the extracellular domain of the NOTCH1 receptor in the endocardium, favoring its interaction with the ligand DELTA4 (DLL4). "Both DLL4 and NOTCH1 gene knockouts affect the proliferation and differentiation of trabecular cardiomyocytes, causing early embryonic death", he adds.

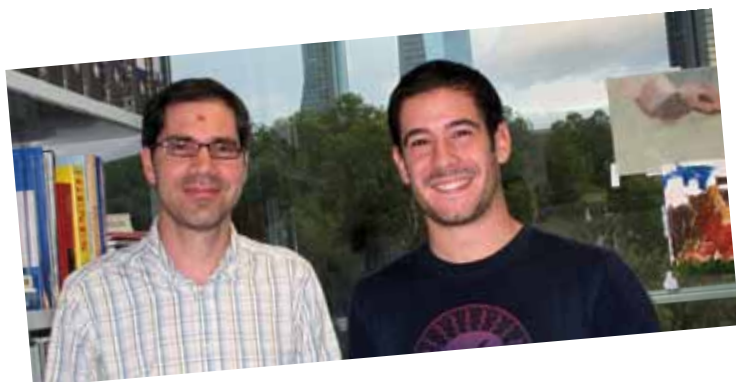
In conclusion, the researchers believe that the essential information provided by this work on ventricular development and maturation opens a new field of research in the pathogenesis of human cardiomyopathies; the group will continue with this line of research.



NATURE COMMUNICATIONS

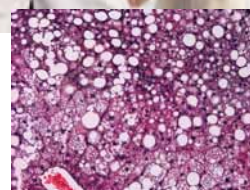
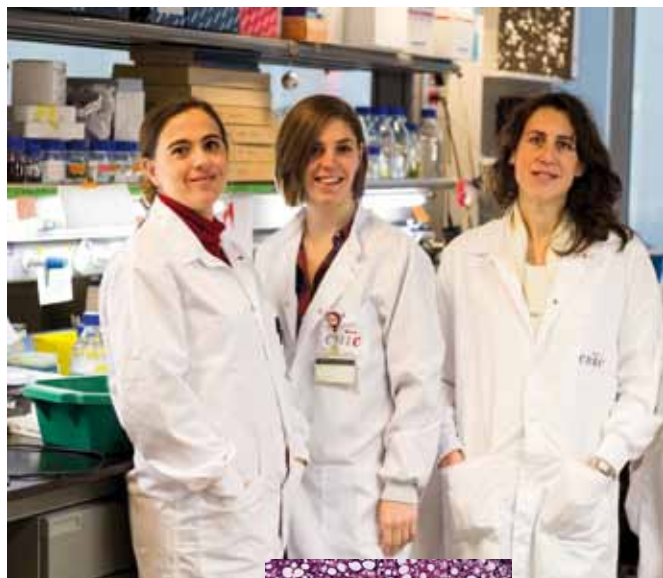
Researchers led by [Dr. Andrés Hidalgo](#) and [Dr. Magdalena Leiva](#) identified a new mechanism through which blood stem cells control both their own proliferation and the characteristics of the niche that houses them. Responsible for this control is the protein E-Selectin Ligand-1 (ESL-1). The authors of this paper, published in *Nature Communications*, saw that this protein is expressed in large amounts in these stem cells and were able to observe that it also controls the production of the cytokine TGF- β by these cells. According to the researchers this is important, because the TGF- β protein has anti-proliferative properties and is essential for preventing the disappearance of these stem cells in some pathological processes, such as certain types of anemia.

They also found that cells deficient in the ESL-1 protein are resistant to different types of cytotoxic or chemotherapeutic agents. These results suggest that the ESL-1 protein may become a target for therapies aimed at improving bone marrow regeneration during chemotherapy or at the expansion of blood stem cells for subsequent donation.



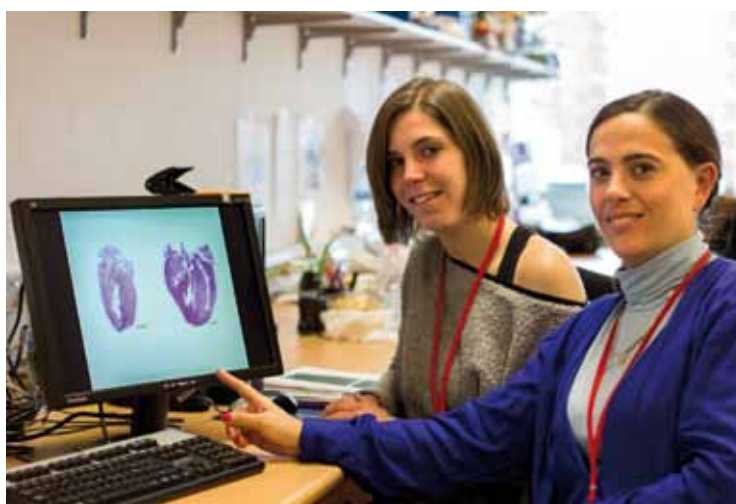
CANCER DISCOVERY

The collaboration between the CNIC and the Center for Applied Medical Research (CIMA) of the University of Navarra allowed the discovery of mechanisms that contribute to the antitumor response of the immune system. The results of this study, published in *Cancer Discovery* and coordinated by [David Sancho and Ignacio Melero](#), show that antigen-presenting cells are responsible for initiating and regulating the immune response to pathogens and tumors; tumors, however, develop mechanisms to escape the control of the immune system by silencing the response of cytotoxic T lymphocytes that eliminate the tumor. According to **David Sancho** of the CNIC, "establishing which antigen-presenting cells promote the anti-tumor immune response can help us design strategies to increase the effectiveness of immunostimulatory antibody treatment and find biomarkers that predict which patients will benefit from that treatment. Our work suggests that these Batf3-dependent dendritic cells may be instrumental in anti-tumor immunotherapy."



NATURE COMMUNICATIONS

In another study published in *Nature Communications* CNIC researchers identified two proteins, p38 gamma and p38 delta, whose function is to control the growth of the heart and its adaptation to high blood pressure or hypertension. "The results not only help to better understand the mechanisms through which heart cells grow and adapt, but may also serve to design new strategies to treat heart failure caused by excessive growth of the heart", says [Dr. Guadalupe Sabio](#), senior author of the paper.



THE EMBO JOURNAL

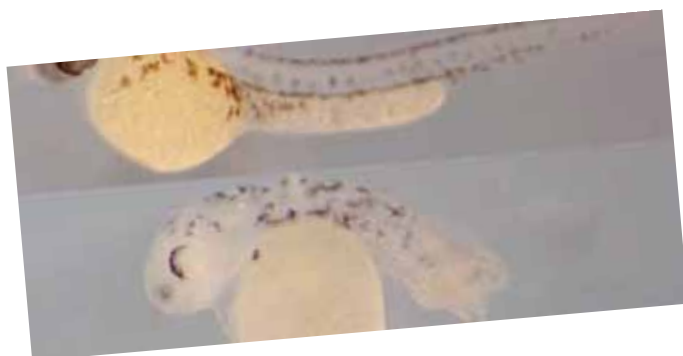
These same two proteins, p38 gamma and p38 delta, are also responsible for controlling the accumulation of fats in the liver, which promotes the development of insulin resistance and diabetes, two events associated with obesity. This was explained in another [article](#) by a group of researchers led by **Dr. Sabio**, who showed that acting on these proteins by specific drugs may become a suitable treatment for fatty liver or steatosis. The results were published in the *EMBO Journal*.



As explained by **Dr. Sabio**, this discovery not only helps to gain a better understanding of the mechanisms involved in the development of the disease, but may also favor the development of treatments and, which is also very important, its prevention.

NATURE GENETICS

Genetic switches regulate the activation of genes during embryonic development to control the generation of tissues and organs. A failure in these switches can cause various diseases. Now a [new study](#) has shown that in order for a group of these switches - the ones that turn on the genes for building structures in vertebrates - to work correctly, they must undergo an epigenetic modification (an alteration of the DNA that does not modify its sequence) during embryonic development. This change is evolutionarily conserved in all vertebrates and is essential for establishing the body plan that all animals of this lineage share. The study, published in *Nature Genetics*, was done by an international group of scientists from the CNIC, the Spanish National Research Council (CSIC), the University of Western Australia and the Radboud University of Nijmegen (The Netherlands).

**JACC**

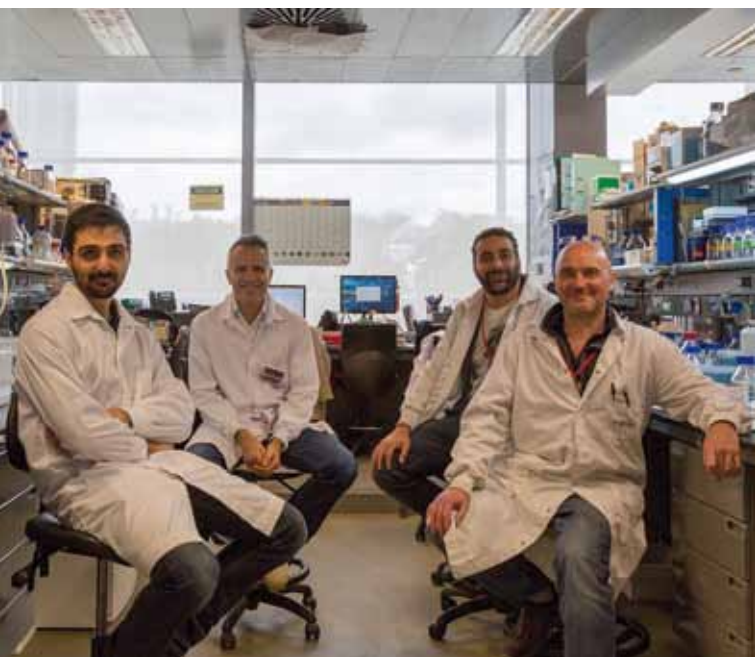
Atherosclerosis is a disease of the blood vessels caused by the accumulation of cholesterol, which makes the blood circulate with greater difficulty through them and increases the risk of causing obstructions, which cause heart attacks and strokes. This is a widespread problem among the population (in Spain, a third of all deaths each year are related to atherosclerosis) and it does not produce symptoms until the damage is often already irreversible. Now researchers of the Aragon Institute of Health Sciences (IACS) in Zaragoza and of the CNIC have described a method for early diagnosis of atherosclerosis. After studying a population of almost 1,500 men between the ages of 40 and 59 (workers at the General Motors factory in Figueruelas, Zaragoza), researchers found cholesterol plaques in the arteries of 72 out of every 100 study participants. The [study](#) shows that the femoral arteries, which are located in the groin and carry blood to the legs, are the best vascular territory for the detection of plaques in association with the classic risk factors for cardiovascular disease such as smoking or high cholesterol levels; and they are also good predictors of the presence of coronary lesions. The study was published in the *Journal of the American College of Cardiology (JACC)*.



CIRCULATION RESEARCH

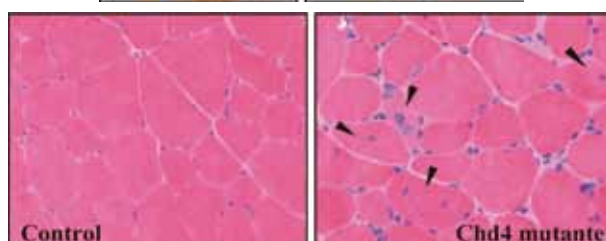
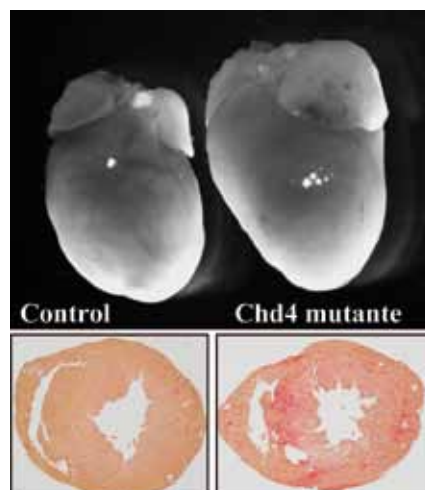
The studies of **Dr. José Luis de la Pompa's** group on the NOTCH signaling pathway have demonstrated the crucial role of this pathway in the development of a fundamental part of the heart, the heart valves, responsible for controlling the unidirectional flow of blood with each heartbeat, and which open and close millions of times during a person's life. Specifically, using genetically engineered mice the researchers showed that this signaling pathway plays an essential role in the entire process of heart valve formation: NOTCH is required for the formation of the primitive valves that operate in the early embryo and, subsequently, for the mature valves to acquire their definitive shape. In this [work](#) a new molecular mechanism regulated by NOTCH was identified that controls tissue proliferation during the late stages of valve development.

The researchers found that alterations in genes in the NOTCH signaling pathway inactivate this control over proliferation, so that the maturing valves grow too much, causing the three leaflets or cusps of the original aortic valve to fuse into two, giving rise to a bicuspid aortic valve (BAV) instead of a tricuspid aortic valve, which is the normal situation. The results were published in *Circulation Research* and may serve to improve the genetic diagnosis and treatment of patients with bicuspid aortic valve, a disease of great prevalence (1-2% of the population) that seriously compromises cardiovascular health.



CELL METABOLISM

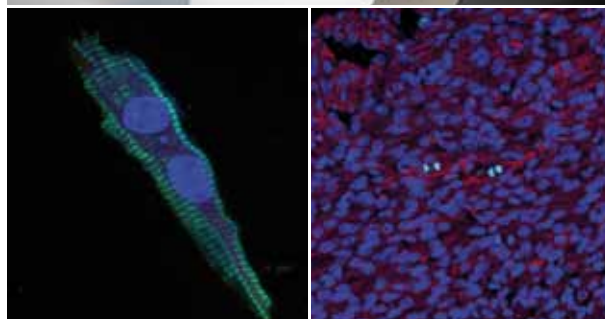
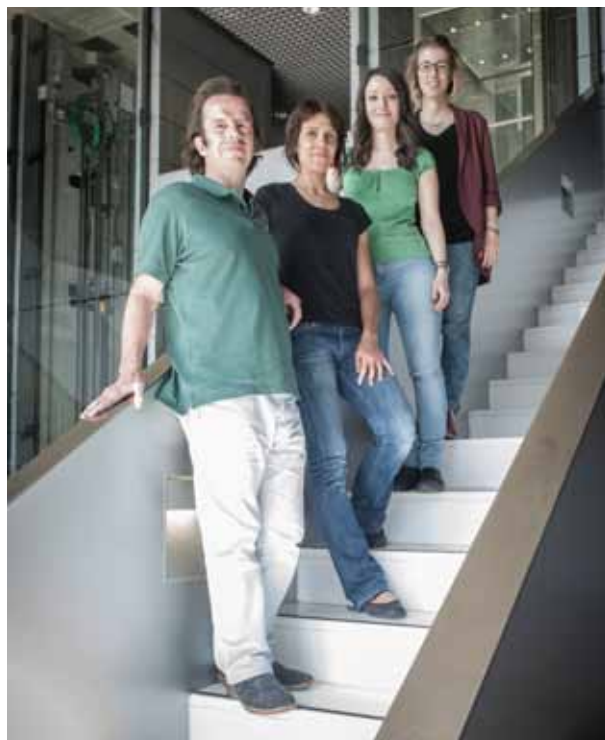
Another [study](#) from the CNIC published in *Cell Metabolism* discovered an essential mechanism in the control of heart and skeletal muscle and their molecular components that, when absent, produces hybrids of these striated muscle tissues that make them incompatible with life. The study, led by **Juan Miguel Redondo**, opens up new hitherto unknown horizons for the study of striated muscle physiology by unveiling the "molecular mechanisms that control the structural identity of cardiac and skeletal tissues". It also may help in the design of future treatments for some cardiac diseases such as certain types of idiopathic dilated cardiomyopathy or polymyositis-type myopathies.



JACC

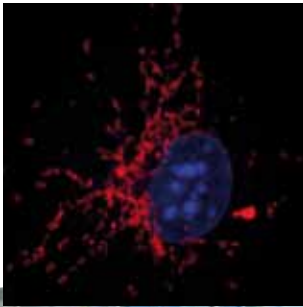
Cardiovascular disease (CVD) is the leading cause of death worldwide. According to the WHO, 17.5 million people die each year because of it. Predicting CVD to be able to prevent it has become a public health priority and, in addition to the "classic" risk factors such as high cholesterol, smoking, sedentary lifestyle, hypertension, etc., new biomarkers are sought that are more effective at predicting cardiovascular risk. Telomeres could be one of them, but according to a [study](#) conducted by **Dr. Valentín Fuster** and **Dr. Vicente Andrés**, telomere length of leukocytes (LTL) in the blood stream does not seem to predict the risk of CVD in asymptomatic individuals effectively. The results were published in **JACC**.

However, according to **Dr. Andrés**, a researcher at the Cardiovascular Research Network of the Institute of Health Carlos III, we must be cautious with the interpretation of these findings, since this study "is like taking a photo at a specific time in the life of an individual, and we still have to determine whether atherosclerotic disease progresses more rapidly in those individuals who initially have shown a shorter LTL and/or a higher short telomere load, or in those subjects in whom the telomere shortening rate during aging is higher". "However", **Dr. Andrés** added, "this important aspect can be elucidated in the follow-up study we intend to carry out in the individuals who participated in this substudy of the PESA project".

**THE JOURNAL OF CELL BIOLOGY**

But telomeres do appear to be important for the regenerative capacity of cardiomyocytes. [Research](#) published in **The Journal of Cell Biology** showed that the regenerative capacity of cardiomyocytes, the muscle cells in the heart that allow the heart to contract, depends largely on the length of their telomeres.

Cardiomyocytes stop dividing a few days after birth and therefore any cells that die later in life due to a heart attack cannot be replaced, which presents a significant difficulty for patient recovery. Researchers led by **Dr. Ignacio Flores** discovered that the loss of this self-renewal capacity of cardiomyocytes is due to shortening of the telomeres. These structures are essential for genome maintenance and begin to shorten soon after birth. The results may point the way to future interventions to increase the regenerative capacity of the heart in mammals.



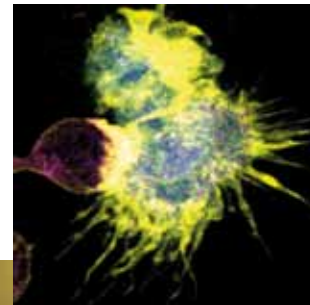
NATURE IMMUNOLOGY

The immune system is equipped with the mechanisms necessary to ward off an attack by bacteria. And we now know that one of the keys to this efficient reaction lies in changes that are triggered in the mitochondrial metabolism, which allow the response of the cells of the immune system to adapt to living or dead bacteria. This was unveiled by researchers from the CNIC, led by **Johan Garaude**, **Rebeca Acín-Pérez**, **José A. Enríquez** and **David Sancho**, in a [paper](#) published in *Nature Immunology*. The findings of this study may also help in the design of vaccines and provide new pharmacological targets for the treatment of infections and inflammatory metabolic disorders.

The study shows how the detection of live bacteria by immune cells called macrophages induces profound structural changes in the organization of the mitochondrial electron transport chain (respiratory chain) in these cells. These changes, explains **Rebeca Acín-Pérez**, "enable the macrophage to redirect metabolic routes to achieve a more efficient metabolism".

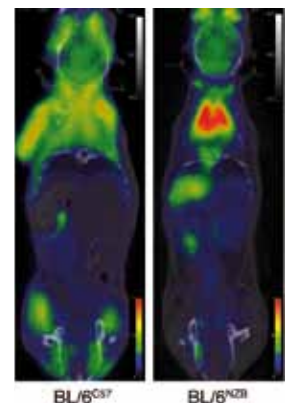
NATURE IMMUNOLOGY

Studies led by **Dr. Francisco Sánchez-Madrid**, Head of the Intercellular Communication Group at the CNIC, allowed defining the key role of a receptor of the immune system in the development of psoriasis and suggest that it could serve as a therapeutic target for the control of this disease. The [study](#), carried out by **Dr. Danay Cibrián** and directed by **Dr. Francisco Sánchez-Madrid**, establishes the role of the leukocyte activation receptor CD69 in the control of amino acid uptake, activation of the aryl hydrocarbon receptor (AhR), and the expression of inflammatory interleukins such as IL-22 in T gamma delta and Th17 cells, indicating that CD69 contributes to the development of psoriasis. The study, published in *Nature Immunology*, also indicates that CD69 may participate in other inflammatory diseases such as atherosclerosis.



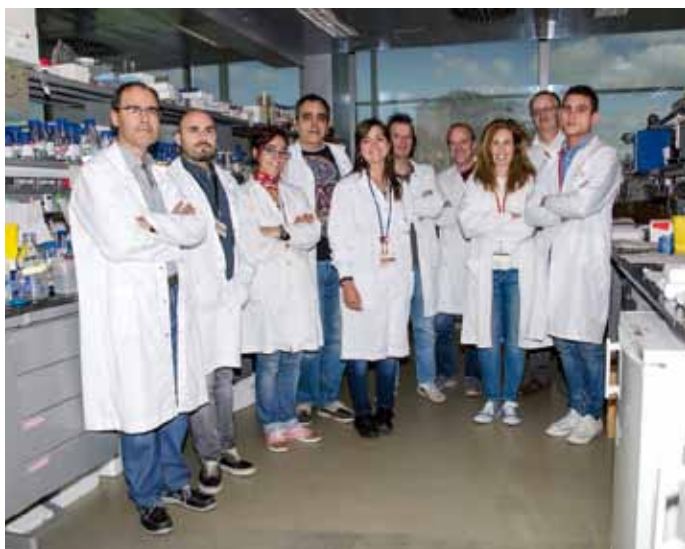
NATURE

Thanks to another [study](#) carried out at the CNIC we now have a better understanding of the physiological differences between individuals and the way in which human beings age, which, according to the study led by **Dr. José Antonio Enríquez**, may be determined well before the aging process begins and the first signs of aging appear. The investigations open the way to the study of common aging-related conditions, such as diabetes, cardiovascular diseases and cancer. Scientists at the CNIC, in partnership with groups at the universities of Zaragoza and Santiago de Compostela and at the



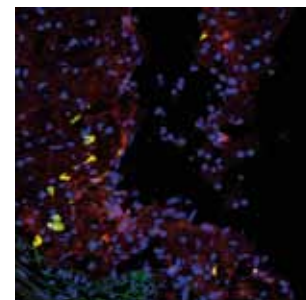
UK's Medical Research Council, have uncovered how the combination and interaction between our two genomes, the nuclear and the mitochondrial genome, triggers a cellular adaptation that has repercussions throughout our lives and determines how we age. The **Nature** study also provides extremely valuable information about how to best use mitochondrial replacement technology. This therapeutic approach, popularly known for producing "three-parent babies", is designed to avoid the transmission of pathogenic mutations from parents to children and has already been approved in the UK.

Of the more than 20,000 human genes, 37 are found not in the cell nucleus but in the mitochondria, small organelles that function as energy factories. The small mitochondrial genome, which we inherit from our mothers, is known as mitochondrial DNA. Like its nuclear equivalent, the mitochondrial genome shows a degree of genetic variability, both in mice and humans. The researchers of the CNIC found that non-pathogenic mitochondrial DNA variants have different impacts on organismal metabolism and aging. The study reveals how "population genetic variation in just a few genes can determine whether we will experience healthy aging". The results represent a major advance in our understanding of the aging process, by showing that "non-pathogenic differences in mitochondrial function have direct repercussions on the rate of aging of an individual", explains **Dr. Enríquez**.



JACC

The CV polypill for secondary prevention is a medication that combines three common medicines: acetylsalicylic acid, a platelet antiaggregant to prevent thrombus formation; atorvastatin, a statin to control cholesterol levels and to stabilize the atherosclerotic plaque; and ramipril, an antihypertensive ACE inhibitor that prevents heart remodeling following an infarct. Now, the results of the **MINERVA** study ("Assessing the Impact of Medication Adherence on Long-Term Cardiovascular Outcomes"), which analyzed the association between medication adherence and long-term major adverse cardiovascular events in patients after myocardial infarction (MI) and patients with atherosclerotic disease, showed a significant association between higher adherence rates and improved patient outcomes and reductions in healthcare costs. The study was published in the **Journal of the American College of Cardiology (JACC)** and was presented at the Congress of the European Society of Cardiology.



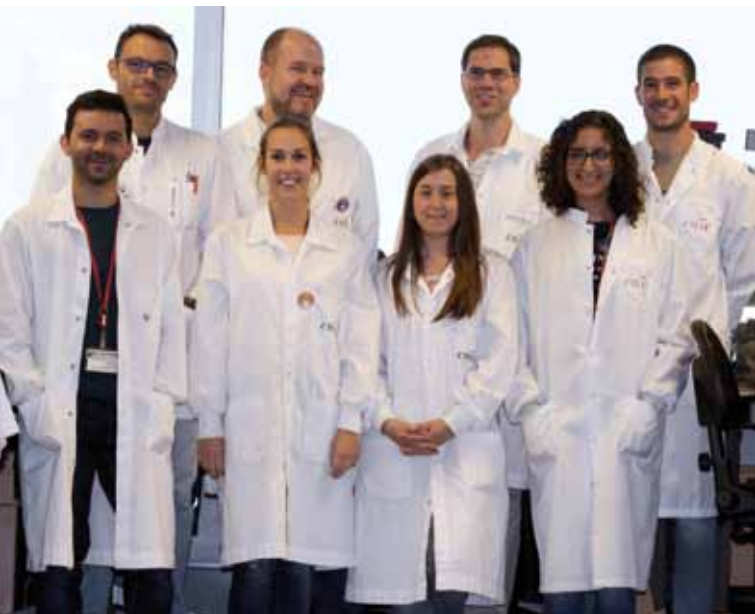
NATURE COMMUNICATIONS

CNIC researchers have identified a new mechanism involved in the development of atherosclerosis. The **study**, published in **Nature Communications**, indicates that nestin+ cells guide the inflammatory response in diseases characterized by chronic inflammation, and therefore could be a new therapeutic target in these conditions. Atherosclerosis arises from fatty deposits in the walls of arteries carrying oxygen-rich blood from the heart to the rest of the body. The disease has a high prevalence worldwide and is a major cause of cardiovascular events. Study leader **Dr. Simón Méndez-Ferrer** explained that atherosclerosis is a chronic inflammatory condition that begins when high levels of blood cholesterol activate the layer of endothelial cells lining the blood vessels. "This activation induces an infiltration of the vessel wall by inflammatory cells, forming the atherosclerotic plaque. When the plaque is weakened, sometimes due to calcification, it can rupture and release its contents into the bloodstream and start a chain reaction that ends in the formation of one or more clots that block blood vessels", explained **Dr. Raquel del Toro**, first author of the study.

IMMUNITY

The group of **David Sancho**, head of the Immunobiology Laboratory, published an [article](#) in *Immunity* that defined mechanisms mediated by a population of immune cells that may be key to improving the design of new vaccines against pathogens that invade us through the skin or mucous membranes, such as microorganisms causing influenza, herpes, tuberculosis, AIDS, dengue fever or cholera, or emerging viruses.

Most existing vaccines are administered parenterally, intramuscularly or subcutaneously, and are not very efficient inducers of CD8+ memory lymphocyte responses; these lymphocytes promote protective immunity at the mucosa or skin surface. Furthermore, dermal or intranasal immunization with viruses such as the smallpox vaccine (vaccinia) has been shown to generate CD8+ tissue-resident memory T lymphocytes (Trm) in the skin and mucous membranes that are very efficient at preventing reinfection. However, it is not known how this process takes place and what its requirements are. This new study showed that a population of antigen-presenting cells (dendritic cells) provides specific signals for the induction and instruction of this type of immunological memory. "The study identifies the differential factors required to improve vaccines designed to induce long term cellular immunity in barrier tissues such as skin and mucous membranes through the generation of Trm lymphocytes. We also identify a subtype of dendritic cells as the appropriate cellular target for immunization. Finally, our study defines some of the essential signals that stimulate the generation of Trm lymphocyte precursors", explains **David Sancho**.

**IMMUNITY**

David Sancho's group, working together with scientists at other national and international centers, also identified a mechanism that allows the *Leishmania* parasite, which causes leishmaniasis, to evade the immune system and thereby produce an infection. The [study](#), published in *Immunity*, shows that a secreted molecule produced by the parasite binds specifically to a receptor called Mincle (Clec4e) expressed on the surface of antigen-presenting cells (dendritic cells), and sabotages their function. There is currently no effective vaccine for leishmaniasis, and the research team speculates that the poor performance of vaccines derived from whole parasite extracts might be due to the presence of the Mincle ligand. Leishmaniasis is transmitted to people through bites of infected phlebotomus sandflies. The disease mostly affects people in tropical and subtropical zones, but is also present in Mediterranean countries, including Spain, where an outbreak occurred near Madrid in 2012.

NATURE

In a [study](#) published in *Nature*, scientists at the CNIC defined the molecular organization underlying energy production in living cells. The discovery sheds light on the regulation of metabolism and presents a milestone in the understanding of the organization of the mitochondrial electron transport chain, which produces energy from nutrient-derived molecules. The study also suggests ways in which different organizations of the mitochondrial electron transport chain may affect metabolism and be linked to the tendency to develop certain diseases.

For many years scientists believed that the structures within mitochondria that permit cell respiration were mixed randomly and had no precise organization. This view held back understanding of mitochondrial respiration and the importance of its regulation in the control of metabolic and cellular stress and its possible role in disease. The new study was carried out by groups led by **professors José Antonio Enríquez** and **Jesús Vázquez**, with first authors **Dr. Sara Cogliati** and **Dr. Enrique Calvo**. Its results, in addition to uncovering the mechanisms that organize the mitochondrial electron transport chain, are a milestone in understanding how different structures of the electron transport chain affect metabolism and the relation of these structures to the risk of developing specific diseases.

**PNAS**

Progeria is a very rare genetic disease, estimated to affect fewer than 400 people worldwide. The disease is caused by a mutation in the gene encoding laminin A (LMNA). The mutation causes incorrect processing of the messenger RNA encoded by the gene, and this results in the production of an anomalous version of the pre-laminin A protein called progerin, which accumulates in the cell nucleus.

Children presenting progeria symptoms can be diagnosed with a genetic test, but as yet there is no effective treatment for the disease, and patients die in the first two decades of life. The cause of death in progeria is principally related to cardiovascular problems, but very little is known about the mechanisms underlying the anomalies that characterize progeria.

But thanks to a [study](#) by the CNIC published in the *Proceedings of the National Academy of Sciences (PNAS)*, defects in the hearts of progeria patients have been identified that appear to be related to an elevated risk of arrhythmias and premature death. The study, coordinated by **Dr. Vicente Andrés**, shows that these risks are linked to anomalies in the transmission of electrical signals in the hearts of individuals with progeria, also known as the Hutchinson-Gilford progeria syndrome (HGPS). Specifically, the study shows for the first time that HGPS patients share similar defects with mice lacking the metalloproteinase ZMPSTE24/FACE1, an experimental model of progeria. "The conduction anomalies in the hearts of progeric mice are accompanied by an altered subcellular location of the protein connexin 43, and similar alterations are seen in the hearts of HGPS patients", comments **Dr. Andrés**. Normally, connexin 43 accumulates at gap junctions—specialized connections between cells that are essential for the correct propagation of electrical impulses. Altered connexin 43 expression is found in several cardiovascular diseases affecting the general population, and is also associated with normal aging. Aberrant connexin 43 expression also provokes electrical alterations in the myocardium that favor the development of arrhythmias. The study showed that in the progeric heart, connexin 43 is incorrectly localized laterally and accumulates in the perinuclear region of the cytoplasm of the cardiomyocytes.

These findings, which were also observed in a mouse model of the disease used by the research team, open the way to research into the development of new treatments to correct these characteristic defects associated with progeria. The study may also provide clues about the mechanisms involved in normal aging and the development of associated cardiovascular disease.

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PARTNERSHIPS TO PROMOTE RESEARCH ON HEART DISEASE

THE CNIC SIGNS **THREE COLLABORATION AGREEMENTS** SHARING THE SAME IDEA: PROMOTING CARDIOVASCULAR RESEARCH OF EXCELLENCE AND TRANSFERRING THE FINDINGS TO THE MAIN BENEFICIARIES: THE PATIENTS

Translational research, the application of basic research for the benefit of patients, and collaboration with other research centers and hospitals are two of the pillars on which the philosophy of the CNIC is based. Therefore, one of the CNIC's objectives is to promote collaborations with other national and international clinical centers. As a result of this continuous search and expansion, the CNIC has signed three new agreements with prestigious

national institutions with different objectives, but with a common idea: promoting cardiovascular research of excellence and transferring the findings to the main beneficiaries: the patients.

One of these agreements is the one that the center directed by **Dr. Valentín Fuster** signed with the Health Research Institute of the Jiménez Díaz Foundation in Madrid (IIS-



FJD). The aim is to develop a joint program that includes translating laboratory findings directly to patients, conducting joint clinical trials, exchanging research staff and clinical staff, and joint training of young resident physicians.

Years ago, the CNIC established a program of collaborations with hospitals of excellence, both in Spain and abroad, in order to apply the progress made in the laboratories of the center to patients suffering from cardiovascular diseases. Each of these programs pursues specific goals and is developed by cardiologists (or other specialists in fields related to cardiovascular disease) who combine research with healthcare tasks in their hospitals.

The FJD university hospital is one of the Spanish hospitals with a long tradition of teaching and research. Through the IIS-FJD, the group Quironsalud-Helios will engage other hospitals in the research and will make all means available for cardiology research to reach the patients in the most direct manner possible.

APPLICATION OF NEW FINDINGS

The main objective of this agreement is to apply new findings by basic research on very specific pathologies, such as acute myocardial infarction and heart failure. To achieve this, initial studies will be conducted in patients to test new therapeutic targets, the jointly developed imaging technology of the myocardium will be applied, and more knowledge of the cardiac health of asymptomatic individuals will be obtained. The agreement also seeks to make a qualitative leap in the training of doctors during their residency. To this end, programs will be developed for cardiologists and other medical specialists to also receive training in the field of cardiovascular research.

Under the direct supervision of **Dr. Valentín Fuster**, general director of the CNIC and director of the Cardiovascular Institute of the Mount Sinai Hospital in New York, the program is coordinated by cardiologist **Borja Ibáñez**, director of the Clinical Research Department at the CNIC and interventional cardiologist at the Jiménez Díaz Foundation, and by **Dr. Carmen Ayuso**, director of the

The CNIC and the Health Research Institute of the Jiménez Díaz Foundation will work together to translate progress made in the laboratory to patients with cardiovascular diseases

The agreement with the Research Institute of the Hospital 12 de Octubre (i + 12) will translate the knowledge acquired in research to clinical practice within the framework of the Valentín Fuster Program





Health Research Institute of the Jiménez Díaz Foundation.

Both professionals will lead the Program's monitoring commission to ensure that the ambitious goals are met and that the project results in improved cardiovascular health of patients.

VALENTÍN FUSTER PROGRAM

With the same aim of promoting high-quality translational research in the area of cardiovascular disease among physicians who combine clinical care activity and research, a formal partnership was signed with the [Research Institute of the Hospital 12 de Octubre \(i+12\)](#) to develop the Valentín Fuster Program.

The project, which will run for the next five years, seeks to translate research results immediately to the clinic in the form of new therapeutic targets and procedures that contribute to improving the evolution of patients and that also serve to prevent these diseases. Likewise, the hospital will transfer the clinical needs of patients and specialists to the CNIC to make progress in the prevention, diagnosis and treatment of these diseases.

The agreement also seeks to promote developments in science and health among professionals, not only in the two institutions, but also in national and international scientific societies. Thus, the main beneficiaries of this program also include other cardiologists and specialists in fields related

to cardiovascular disease of the Spanish National Health System, since the project is multidisciplinary in nature.

Dr. Héctor Bueno, a cardiologist with a broad national and international experience in clinical research, scientific director of the cardiovascular area of the 12 de Octubre University Hospital and of the Multidisciplinary Translational Cardiovascular Research Group of the CNIC, and president of the Acute Cardiovascular Care Association of the [European Society of Cardiology](#), leads the multidisciplinary team that will work together with members of the cardiology department and other hospital facilities, and with researchers from the CNIC and other renowned national and international institutions.

CARDIOVASCULAR IMAGING

Furthermore, with the aim of positioning itself as an international leader in biomedical imaging research, the CNIC signed an agreement with the Basque [Center for Cooperative Research in Biomaterials biomaGUNE](#). Through this collaboration, part of the Centers' scientific-technological skills and equipment will be integrated, which will allow it to be recognized as a Singular Scientific-Technological Infrastructure (SSTI) by the Spanish Government.

The objective of the open-ended agreement is to offer the scientific-industrial community a unique infrastructure for

biomedical imaging, to create synergies between the two centers through joint projects, to opt for more competitive financing programs, and to promote the exchange of researchers to carry out scientific training programs of excellence.

CIC biomaGUNE, led by **Luis Liz Marzán**, has a preclinical molecular imaging facility that has formed part of the Spanish Government's SSTI since 2011. The facility is equipped with a particle accelerator (cyclotron) capable of converting stable chemical elements into short-lived radioisotopes that can be incorporated into any molecule without altering its properties, and that makes its identification possible. Thanks to this procedure, researchers can track the molecule inside living organisms in a non-invasive manner using tomographic cameras. This equipment, one of the few in Spain and the only one in the Basque Country, is a powerful diagnostic tool that opens the way to the discovery of new drugs. In addition, the facility is equipped with one of Europe's most powerful magnetic resonance imaging (MRI) scanners, which enables obtaining three-dimensional images to visualize the function of the body at high resolution.

The CNIC maintains an unequivocal commitment to the use of imaging technology as a fundamental tool to better understand cardiovascular processes and pathologies. For this purpose, the CNIC has an immense variety of technological imaging resources, ranging from cutting-edge microscopy techniques, high-content screening and high-throughput technologies, imaging equipment for experimental models (high field resonance, micro PET/CT, fluoroscopic imaging) and a clinical imaging setup with one of the few hybrid PET-MRI systems for human use, to a CAT multidetector and state-of-the-art ultrasound equipment.

The sharing of these unique technological and complementary imaging resources of both centers reflects a very ambitious commitment that should position this dispersed SSTI at the forefront of biomedical imaging worldwide.

Accordingly, the first call for proposals to access the **ReDIB** Singular Scientific-Technological Infrastructure (SSTI) has been launched. The equipment available at the SSTI, one of few such facilities in Europe, constitutes a uniquely powerful diagnostic tool in molecular and functional imaging, as well as in advanced and high-throughput imaging. ReDIB is composed of two nodes, located at the CNIC and the CIC biomaGUNE.

The CNIC and the CIC biomaGUNE offer the scientific-industrial community a unique infrastructure for biomedical imaging and create synergies between the two centers through joint projects





THE POLYPILL IN THE EUROPEAN PARLIAMENT

THIS INNOVATIVE PUBLIC-PRIVATE STRATEGY RECEIVED PRAISE AT AN EVENT HELD IN THE EUROPEAN PARLIAMENT

Cardiovascular disease is the leading cause of death worldwide and people with a history of myocardial infarction are more likely to die of other cardiovascular causes within a year. Twenty percent of chronic patients do not start prescribed treatment and less than fifty percent of patients who have suffered a first cardiovascular event continue to take their medication after the first six months.

Given that not taking the prescribed medication to prevent further cardiovascular disease severely increases overall

cardiovascular risk, Ferrer and the CNIC successfully developed an innovative polypill within the framework of a public-private partnership. The CV polypill for secondary prevention is a medication that combines three common medicines: acetylsalicylic acid, a platelet antiaggregant to prevent thrombus formation; atorvastatin, a statin to control cholesterol levels and to stabilize the atherosclerotic plaque; and ramipril, an antihypertensive ACE inhibitor that prevents heart remodeling following an infarct. Throughout, the goal of the project has been to reduce

the problems that people may experience when several drugs are prescribed. In addition, it offers physicians cost-effective tools to treat patients better, which reduces the social burden and loss of personal productivity by preventing major cardiovascular events and deaths. Supported by the 7th European Framework Program and **Horizon 2020 funding** (centered on the development of the already completed important **FOCUS** study and the ongoing **SECURE** trial), this leading-edge approach has been approved in fifteen European countries and is already being commercialized across Europe and Latin America.

In an event held in the European Parliament and hosted by MEPs **Francesc Gambús** (Spain, PPE) and **Aldo Patriciello** (Italy, PPE), in cooperation with the National Center for Cardiovascular Research Carlos III (CNIC) and the Barcelona-based pharmaceutical company Ferrer, the risks posed in today's society by inadequate treatment were addressed. Inadequate treatment results in poor adherence among people suffering from cardiovascular disease, which threatens their future health and well-being.

Professor Valentín Fuster, general director of the CNIC in Madrid and Mount Sinai Heart in New York, and leader of the CNIC-Ferrer Polypill project, highlighted the clinical challenges presented by secondary prevention of cardiovascular risk.

In this context, the EU Framework Program Horizon 2020 is investing in prioritizing research and innovation to improve health in chronic diseases such as cardiovascular diseases. And the EUROASPIRE IV study has highlighted the need for a new approach to cardiovascular prevention. **Professor Fuster** called on the health systems to consider alternatives based on the Polypill as a potential means to achieve innovative and effective improvements in established disease areas. "Focusing on the simplest challenge, if we present medicines in a way that people can understand and incorporate into their daily lives, it is

possible to make much more progress in cost-effective public health improvement than to start drug discovery processes", commented **Dr. Fuster**.

Speakers also included representatives of the European Commission, the European Association for Cardiovascular Prevention and Rehabilitation, CNIC-Ferrer, and **Margaretha Hamrin**, head of the Norwegian Familial Hypercholesterolemia Foundation, who presented the personal perspective of patients living at increased risk of secondary cardiovascular disease.

Hamrin commented: "Handling the reality of living in the shadow of cardiovascular disease can be very difficult. Life doesn't stop and it is essential that incorporating taking medicine into a busy schedule is made as easy as possible. Using a polypill, which allows you to take all your medicines at once, can offer reassurance and freedom from anxiety and further risk. It contributes to saving lives by increasing adherence to treatments for chronic diseases".

Antoni Villaró, CEO of **Ferrer**, commented: "Innovation focused on addressing the needs of people is critical in the development of new treatments. This task can be made easier if it is based on an effective dialogue and collaborative efforts between different levels of expertise. The successful development of the Polypill is a very real example of what is possible when you bring public and private groups together. It is an example of the future of research that supports the sustainability of the European Health System".

Along these same lines, MEPs **Gambús** and **Patriciello** highlighted the Polypill strategy as a solid example of innovation. They also described it as a successful public-private partnership in Europe at a time of downward pressure on healthcare budgets. Both MEPs underlined the importance of ensuring an effective management of cardiovascular disease, which remains a key priority for healthcare decision makers.



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#100AñosHeparina



**SPAIN, WORLD LEADER IN THE PRODUCTION OF HEPARIN AND
IN THE RESEARCH INTO NEW USES FOR THIS DRUG**

THE PRO-CNIC FOUNDATION CELEBRATES 100 YEARS OF **HEPARIN**

CARDIOLOGY IS ONE OF THE MEDICAL SPECIALTIES THAT BENEFIT MOST FROM THE USE OF THIS DRUG, WHICH WAS **DECLARED AN ESSENTIAL DRUG** BY THE WORLD HEALTH ORGANIZATION (WHO)

Heparin, the world's most widely used natural anticoagulant, saves some 100 million lives a year and is celebrating the centennial of its discovery this year. To commemorate this, the [Pro-CNIC Foundation](#) (Spanish National Center for Cardiovascular Research) and [Biobélica](#), in collaboration with other scientific institutions—Sanofi, Laboratorios Rovi, the [Cotec Foundation for Innovation](#) and [Marca España](#)— and under the honorary patronage of **King Felipe VI**, organized an event at the Institute of Health Carlos III in which the role of Spain in the global production of heparin and the research into new applications of this drug was highlighted.

The institutional event, which had a scientific character, included the participation of **Dr. Valentín Fuster**, director of the Cardiology Unit at Mount Sinai Hospital in New York (USA) and general director of the National Center for Cardiovascular Research Carlos III of Madrid, **Dr. Robert Daniel Rosenberg** of [Beth Israel Deaconess Medical Center](#) in Boston (USA), Secretary of State for R&D and Innovation [Carmen Vela](#), and **Jorge Barrero**, general director of the COTEC Foundation for Technological Innovation.

Heparin is an antithrombic and anticoagulant drug that was declared an essential drug by the World Health Organization (WHO). "Heparin is an advance in medicine as important as penicillin, and its discovery represented an incredible step forward for the health of the general population", explained **Dr. Fuster**. He added: "Heparin was the first drug we had to prevent and treat blood clots: it was a pioneer. Without heparin, modern medicine would not exist". It does not come as a surprise that cardiology is one of the medical specialties that benefitted most from the use of this drug.

Spain began producing heparin in 1975, the same year that the use of heparin became prevalent in clinical practice, and it became the main producer in the Western world. Today Spain produces 20% of the heparin administered worldwide. "I feel proud of the contribution of Spain to the development of this drug, which is incredibly important in the history of medicine", added **Dr. Fuster**.

The celebration of the centennial of heparin reunited all sectors and agents associated with this drug for the prevention and treatment of thrombosis, which saves 100 million lives each year. For example, heparin is the treatment of choice for the prevention of venous thrombosis, a pathologic process which causes one in four deaths in the world, that is, more than cancer, HIV or traffic accidents. In this regard, **Dr. Valentín Fuster** pointed out that "venous thrombosis is probably the most important cause of mortality in the world".

Heparin is an essential drug for a large number of medical specialties, such as general and vascular surgery, emergency medicine, traumatology, gynecology, oncology, hematology and cardiology. **Dr. Rosenberg** from the Beth Israel Deaconess Medical Center, one of the world's foremost experts on heparin, commented that "as we are

researching the functions carried out by each part of the molecule, we will discover new uses for it".

In this regard, and although it is 100 years old, heparin remains an essential drug in medical practice, in particular in modern surgery. Additional uses in malaria, cystic fibrosis, prevention of repeated miscarriages and cancer treatment are also under study. **Carmen Vela** affirmed that "the history of heparin is a success story which must encourage us to keep moving forward on the path of innovation, research and healthcare".

Scientists attribute a growing number of biological properties to heparin due to its capacity to interact with a large number of proteins (extracellular matrix proteins, enzymes, enzyme inhibitors, growth factors, proteins of microbial origin, etc.). The roadmap to advance towards these other uses includes finding a modified heparin molecule that does not have hemorrhagic and anticoagulant properties, and to develop all its properties that are not related to coagulation, such as for example antitumor, antiviral, and anti-inflammatory properties, to their full potential. At the international level, the use of heparin is among others being investigated for the treatment of cancer, chronic obstructive pulmonary disease (COPD), organ transplantation, arthritis, asthma and pulmonary emphysema. For that matter, **Jorge Barrero**, General Director of the COTEC Foundation, stressed that "it would be a good thing if the research on heparin being currently done in Spain could be translated to other types of molecules".

In addition, experts do not rule out the possibility that, as with aspirin, heparin will experience a "second life", since it has been observed that it may have applications other than the classic ones. Aspirin was in fact initially marketed as an anti-inflammatory or analgesic drug, whereas today it is mainly used for the prevention of myocardial infarction.

CONTROVERSY REGARDING ITS DISCOVERY

Heparin was discovered in 1916 by the American **Jay McLean**—then a young medical student at [Johns Hopkins University](#) in Baltimore (USA)—. **McLean** discovered heparin during a study of canine liver cells, and he was able to isolate this powerful anticoagulant. However, others attribute the finding to the eminent American scientist **William Howell**, who named the drug after the Greek word for liver: 'hêpar'.

McLean had to leave the university in 1917 and left the research to his tutor, who, according to different monographs, developed another fat-soluble anticoagulant that was apparently distinct from the one isolated by **McLean**. In 1926, **Howell** introduced further improvements to the protocol, and the final result was a compound different from the previous ones, including the one discovered in 1916 by **McLean**; the latter, however, proclaimed for many years, and publicly recounted in journals and wherever he was invited to give a lecture, to have discovered heparin.



THE MOST HEART-HEALTHY APP: 'THE CIRCLE OF HEALTH'

THE **INTERNATIONAL VERSION** OF THE APP IS NOW AVAILABLE
(IN ENGLISH AND IN SPANISH)

Any help to improve health is welcome and, in an era dominated by electronic gadgets, a mobile application designed to improve the cardiovascular health of the population is an obvious choice. The 'Circle of Health' is an app designed to help prevent cardiovascular disease, which is currently the number one cause of mortality in the world. The app aims to reduce cardiovascular disease-related mortality worldwide and to reduce the

global epidemics of coronary heart disease, infarction and stroke. English and Spanish versions of the app can be downloaded at www.thecircleofhealth.org or on Android and iOS platforms.

Cardiovascular disease can be largely prevented. Most cases arise due to one or more of six risk factors that can be prevented or reduced with simple modifications

of lifestyle and behavior. These six risk factors are: high cholesterol and diabetes (chemical), obesity and high blood pressure (physical), and smoking and lack of exercise (behavioral). These six factors account for 90 percent of heart attacks and strokes”, says **Dr. Valentin Fuster**, General Director of the CNIC and proponent of this tool.

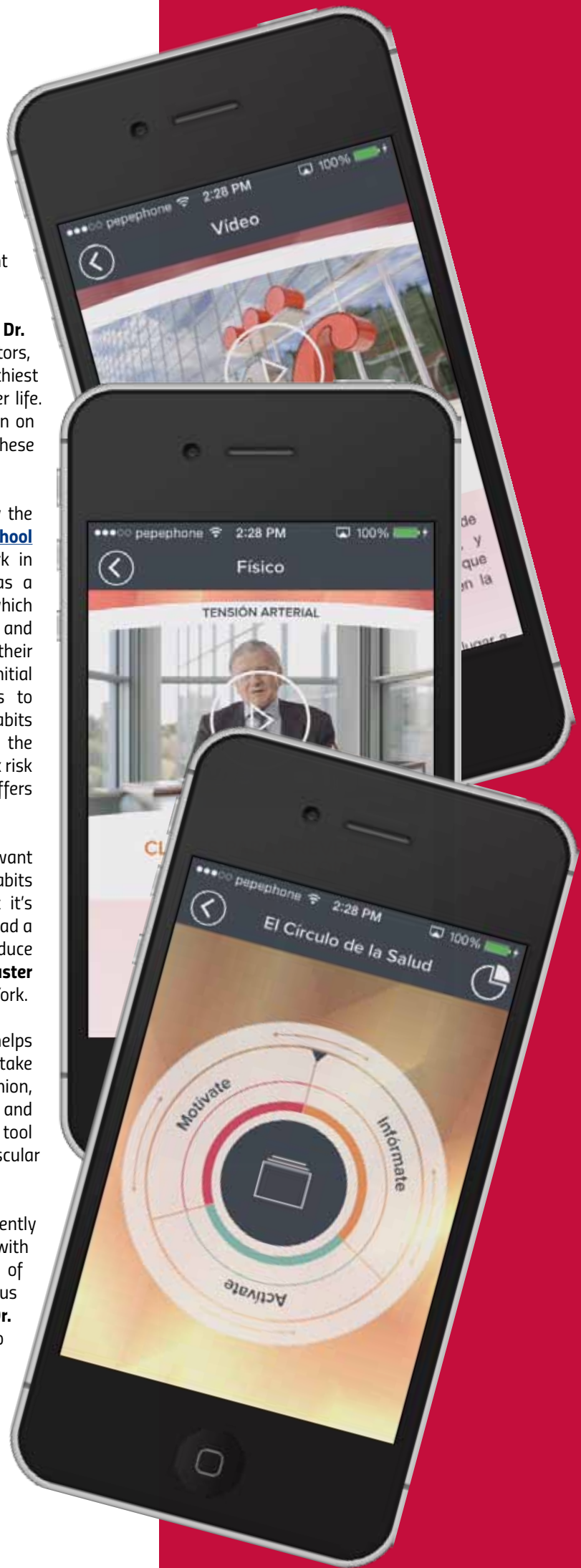
Using this app, users learn directly from **Dr. Fuster** about the six cardiovascular risk factors, how to prevent or manage them in the healthiest way, and how to live a healthier and longer life. In short, the app gives the user information on how to measure, prevent, fight and reduce these risk factors.

To facilitate its use, the app, developed by the [Pro-CNIC Foundation](#) and the [Icahn School of Medicine at Mount Sinai](#) in New York in collaboration with [Wake App Health](#), has a unique circular multimedia interface which incorporates interactive video, audio, and educational graphics. Users can evaluate their cardiovascular health with a simple initial questionnaire and thus obtain the keys to improving their health by reducing bad habits and promoting healthy habits. In addition, the app provides clues on how to prevent the six risk factors and take care of the heart, and offers weekly challenges to live a healthier life.

“This mobile app is for those people who want to improve their health and lifestyle habits including diet, physical exercise, etc.; but it’s also a very useful tool for those who have had a heart attack, stroke, or artery disease to reduce their chances of a future event,” said **Dr. Fuster** during the presentation of the app in New York.

According to **Dr. Fuster**, “the information helps make the best health decisions and thus take care of the heart. It’s that simple”. In his opinion, cardiovascular disease can be prevented and anyone is able to do so. “This app is a tool available to anyone to promote cardiovascular health based on knowledge”.

It has been calculated that there are currently more than 6 billion people in the world with mobile phones, and that nearly 2 billion of them have smartphones. Given the enormous popularity of smartphones and tablets, **Dr. Fuster** believes there is no better way to reach people than via their mobile devices to promote healthy habits. “Preventing and managing cardiovascular disease can be as simple as consulting one of these devices that are always within our reach,” added **Dr. Fuster**.



CNIC OPENS ITS DOORS TO THE YOUNGEST AMONG US

For the fifth consecutive year, the CNIC participated in the Madrid Science Week. This year, two new activities were developed: 'A family day at the CNIC', intended for the little ones, and the one-day meeting 'Get closer to CNIC research' aimed at students from Junior and Senior High Schools.

'A FAMILY DAY': SCIENCE FROM UP CLOSE FOR CHILDREN

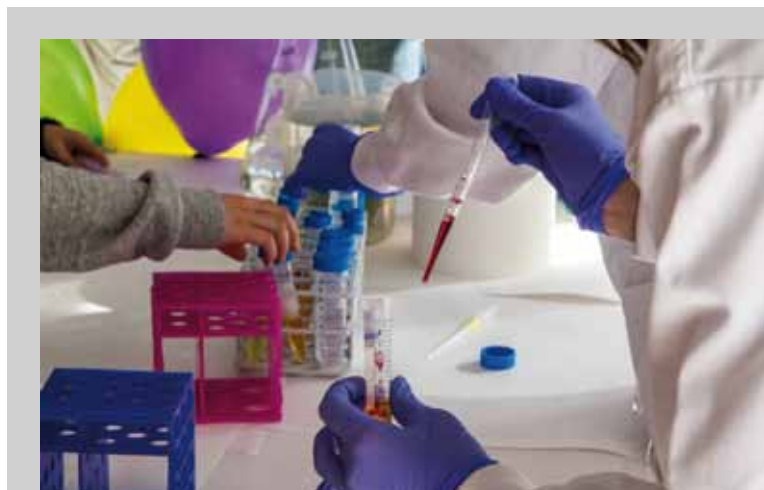
Seventy children and their parents were able to discover some of the best kept secrets of the CNIC researchers for the second consecutive year. The objective of 'A family day at the CNIC', an activity for children from 4 to 14 years and whose motto was "The magic of food: use it to take care of your heart", is to bring science closer to some of our future scientists. Through theater, entertainment and science workshops the children were having a good time, but they also learned from the experiments carried out by some volunteer scientists of the CNIC.

The children were having fun, but learned at the same time, thanks to the workshops specifically prepared for each age group. Thus, in the workshop called "Vegetables are fun", the kids learned not only that fruits and vegetables are necessary ingredients of a balanced diet, but also that their chemical compounds and nutrients, which make them unique and attribute certain beneficial properties to health, have different colors: green, red, blue, white, purple, etc. And in the workshop "Milk of many colors" they painted a painting with colorants in which they could see that milk contains water, but also fats.

We are surrounded by microbes. Good microbes, bad microbes and, most of all, microbes that are neither good nor bad. But how many bacteria do we have on our hands? On a Petri dish, which all children could take home, they could see how colonies of bacteria grow. And at the same time they learned how important it is to wash your hands.

And in the workshop called "Fermentation" they studied how yeasts, which are microscopic eukaryotic organisms classified as fungi, feed; the equipment and chemicals they used were a bottle, a balloon, a bit of sugar, an elastic band and warm water. Meanwhile, in the workshop called "Purify Tomato DNA", the kids investigated how to break the tomato cells in such a way that the DNA is released and can be obtained.

Other workshops were "Our Breathing and the Plants," which served to learn that, when breathing, we inhale O₂ and exhale CO₂, whereas plants, unlike animals, absorb CO₂ from the environment and release O₂; and "Magical antibodies", in which the children were explained by use of magic how the immune response works. And finally, the kids could measure their pulse using modeling clay, a toothpick and a watch.





ONE-DAY MEETING 'ACÉRCATE'

How can you make a career in science? Why do research in Spain and not abroad, where there are more resources? Does a fellowship provide enough money to live on? Do you need to leave Spain to develop a good scientific career? These were some of the questions that the nearly 200 students of Junior and Senior High Schools raised during the one-day meeting '[Get closer \('acércate' in Spanish\) to CNIC research](#)', which was held at the CNIC on the occasion of the Science Week.

Students from the [Bilingual Zola Villafranca School](#), the [Nueva Castilla School](#), the [Zurbarán School](#), the [Santa María del Camino School](#) and the [Vallmont School](#) participated in a new edition of the one-day meeting 'Get closer to CNIC research', during which they were not only able to learn how to become a researcher or what a research career consists of, but also to voice some of their concerns.

One of the objectives of the CNIC is to attract young talent towards the most advanced cardiovascular research. The Acércate Program invites eight brilliant senior high school students from across the country to spend two weeks at the center. However, interest in research can be awakened earlier, and the Science Week offers an opportunity for this.

The day began by showing a video about the Acércate Program. Next, researchers **María del Valle Montalvo** and **Leticia Herrera Melle** explained what it is like to do your PhD at the CNIC, **Rebeca Acín** talked about the steps necessary to become a postdoc and **Guadalupe Sabio**, who heads a research group at the CNIC —whose main line of research is the role of stress-activated kinases in the development of diseases associated with obesity such as cardiovascular disease, diabetes and liver cancer— commented on what it means to be a group leader.

But it was during the round table, which was attended by the four researchers and **Julia Redondo**, Scientific Management Director at the CNIC, when the students could ask and comment about the program and a career in research. It was encouraging that half of the participants in the meeting were interested in science, and they were all given information about the different training programs available at the CNIC.



Fundación Centro Nacional
de Investigaciones Cardiovasculares Carlos III

THE CNIC, "SETTING THE STANDARD FOR RESEARCH IN SPAIN AND EUROPE"

"Setting the standard for research in Spain and Europe". This is how **Carlos Moedas**, European Union Commissioner for Research, Science and Innovation defined the Spanish National Center for Cardiovascular Research (CNIC) Carlos III during his visit last October. Accompanied by **Dr. Jesús Fernández Crespo**, director of the **Institute of Health Carlos III**; **Dr. Valentín Fuster**, general director of the CNIC; **Luis de Carlos Bertrán**, president of the **Pro-CNIC Foundation**; and **Aránzazu Beristain**, head of the Representation of the European Commission in Spain, the commissioner had the

opportunity to meet CNIC researchers in person and learn about the work they do.

The commissioner also said that since 2007 the European Union (EU) has invested 1 billion euros in research on cardiovascular diseases in the framework of its R & D programs, such as the current Horizon 2020 program. In this regard, **Dr. Fuster** pointed out that cardiovascular diseases today are still the main cause of death worldwide.



CNIC PROJECTS

Dr. Fuster explained to the commissioner about the progress and projects carried out at the CNIC, while the president of the **Pro-CNIC Foundation**, which channels the private contributions to the CNIC, gave a brief presentation of the **Pro-CNIC Foundation**, which was fundamental for this center to become a leading institution worldwide, as evidenced by the recent renovation of its status as a Severo Ochoa Center of Excellence.

Despite the crisis, Acciona, BBVA, Endesa, the Abertis Foundation, the Mapfre Foundation, the Mutua Madrileña Foundation, the Ramón Areces Foundation, the Repsol Foundation, Gas Natural Fenosa, Inditex, la Caixa, Prisa, Banco Santander and Telefónica continued to support research programs of the CNIC. Through its Board of Trustees the companies not only provide funds, but also

participate in the decision making and organization of the center. In this way, the private sector is involved, together with the CNIC, in the fight against cardiovascular disease.

Luis de Carlos stressed during the meeting that the contribution by companies is not only a strong commitment to R&D and Innovation, but also “a firm commitment to a matter of great social interest: the health and quality of life of the Spanish people”.

Some of the clinical projects carried out at the CNIC that stand out are the Metocard study; the development of the polypill, a drug that combines the three medicines that must be taken after suffering a heart attack in a single tablet; and the TAN SNIP project, which the CNIC is developing in collaboration with other international centers and that seeks to design tools that take the prevention and establishment of prognosis of cardiovascular disease one step further through noninvasive diagnostic imaging techniques.

In addition, accompanied by **Drs. Borja Ibáñez** and **Vicente Andrés**, the commissioner visited the center’s facilities. He was first received by researchers **Almudena Ramiro**, head of the B lymphocyte Biology Group; **Rui Benedito**, head of the Molecular Genetics of Angiogenesis Group; and **Jacob Fog Bentzon**, head of the Experimental Pathology of Atherosclerosis Group, who explained in person some of the research lines that are being developed at the CNIC.

The commissioner then visited the CNIC’s Human Cardiovascular Imaging Laboratory, located at the Hospital Carlos III, which has the most advanced cardiovascular imaging technology, such as the hybrid TF PET/MRI Ingenuity technology and the new MPI (Magnetic Particle Imaging) modality, which uses nanoparticles to obtain extraordinarily sensitive, high temporal resolution images of the blood flow at the molecular level. **Dr. Gonzalo Pizarro** accompanied the commissioner and explained some of the projects that are being carried out thanks to this leading-edge technology.





THE CNIC IS AGAIN ACCREDITED AS A "SEVERO OCHOA" CENTER OF EXCELLENCE

THE STATE SECRETARIAT
FOR R&D AND INNOVATION
PUT THE CNIC ON CENTER STAGE
FOR **"PLACING SPANISH SCIENCE
IN A PROMINENT POSITION
IN SPITE OF ITS YOUTH"**

The [Ministry of Economy and Competitiveness](#) renewed in 2015 the status of the National Center for Cardiovascular Research Carlos III (CNIC) as a "Severo Ochoa" Center of Excellence, a distinction that had already been granted in 2011. Renewal was granted after a highly positive evaluation process following analysis of the strategic research plan 2016-2019 and the milestones achieved during the previous accreditation period.



EXCELENCIA SEVERO OCHOA

The conclusions of the report issued by the call's Scientific Committee and ratified by the Evaluation Commission put the CNIC on center stage for "placing Spanish science in a prominent position in spite of its youth". They also indicate that the CNIC is an example "for its vision to strengthen collaboration between basic and clinical researchers" and for its "outstanding guidance and leadership in these difficult times, which has made it a world leader".

The "Severo Ochoa" Center of Excellence Award aims to fund and accredit public research centers in any area of science that demonstrate scientific leadership and impact at an international level, and that actively collaborate with their social and business environment. The "Severo Ochoa" Centers of Excellence are organizational structures that have highly competitive frontier research programs that are among the best in the world in their respective fields of science.

The evaluation and selection process is carried out by an independent International Scientific Committee composed of renowned high-impact researchers. Certification is valid for four years, with the possibility of renewal. It involves a grant of four million euros for this period. This funding has a high degree of flexibility and its use must be determined by duly justified strategic criteria for the accredited center.

The CNIC meets the required standards of excellence, which are characterized by:

- Having a high impact and level of competitiveness in its field of activity in the international scientific arena.
- Submitting its research activities to periodic assessment by external and independent scientific committees.
- Carrying out its research activities under a strategic program designed to generate frontier knowledge.
- Training, selecting and attracting human resources at the international level.
- Maintaining active collaboration and exchange agreements at the institutional level with high-level research centers.
- Working on enhancing the transfer and dissemination of knowledge to society.

The benefits of accreditation also include priority access to other initiatives of the State Secretariat for Research, Development and Innovation for the promotion of research, provided that the applicable principles of transparency and competition are observed, a boost in reputation, and a social and scientific recognition that will make them stand out when trying to obtain sponsorships.

The new call confirms the Government's commitment to high-impact research in the public sector. The accredited centers stand out for the international renown of their scientific contributions, their innovative capacity and their strong ties to the business sector. They are, moreover, international centers of reference capable of attracting international talent. In the words of **Dr. Valentín Fuster**, general director of the center, "this recognition is a great boost for the CNIC and for Spanish science in general."

SCIENTIFIC LEADERSHIP

"Severo Ochoa" Centers of Excellence must have a scientific director who must be a researcher of very high standing among his or her peers, and who also has a substantial capacity for leadership in the organization of research - as is the case for **Dr. Fuster**. In addition, the "Severo Ochoa" Centers of Excellence must be centers of reference and clear exponents of the quality and importance of frontier scientific research carried out in Spain. As such, they must serve to lead and give impetus to our research system as a whole and its international projection.

52 MILLION

The total investment in this round of awards was 52 million euros, 32 million more than last year, and this shows the strong commitment of the State Secretariat for R&D and Innovation to excellence in research and innovation. The three centers that obtained the "Severo Ochoa" award for the first time are the Basque Center on Cognition, Brain and Language; the Institute of Material Science of Barcelona of the Spanish National Research Council (CSIC); and the Center for Research in Agricultural Genomics (CRAG), a consortium formed by the CSIC, the Institute of Agroalimentary Research and Technology (IRTA), the Autonomous University of Barcelona (UAB), and the University of Barcelona (UB).

The "Severo Ochoa" Centers of Excellence are organizational structures that have highly competitive frontier research programs that are among the best in the world in their respective fields of science

cnic AWARDS AND FELLOWSHIPS

SEVERO OCHOA PRIZE

The Ferrer Research Foundation awarded the **Severo Ochoa Prize for Biomedical Research** to **Dr. Valentín Fuster**, general director of the CNIC and director of the Cardiovascular Institute of Mount Sinai Medical Center in New York, for his work in the field of prevention and treatment of cardiovascular disease. The Severo Ochoa Prize for Biomedical Research is given to those who make highly innovative contributions to the field of biomedicine and has been awarded in alternate years since 1985. The Secretary of State for Research, Development and Innovation, **Carmen Vela**, presented the award.

NAOS STRATEGY AWARD 2015

Acciona's "Health and Wellbeing" program, a comprehensive plan that promotes healthy eating habits and physical exercise among employees of the company, was implemented in 2012 and enjoyed the counsel of **Dr. Valentín Fuster** (through the **Pro-CNIC Foundation**), the Spanish Nutrition Foundation and the Spanish National Center for Cardiovascular Research. The program received the NAOS Workplace Strategy Award 2015 from the Ministry of Health, through the Spanish Agency for consumer Affairs, Food Safety and Nutrition. The program first launched a phase of assessment of the needs of the workforce. Once these were analyzed, measures were developed focused on three key areas: preventive medicine, exercise and healthy nutrition. The NAOS Strategy Awards recognize those programs, interventions and other initiatives that, as in the case of the "Health and Wellbeing" program, help promote healthy lifestyles to combat obesity through the promotion of a healthy diet and regular physical exercise.



IX Premios
ESTRATEGIA NAOS 2015



SEBBM-BIOTOOLS YOUNG INVESTIGATOR AWARD

Guadalupe Sabio received the **SEBBM-BIOTOOLS** Young Investigator Award, given each year by the Spanish Society for Biochemistry and Molecular Biology (SEBBM). The aim of this award is to recognize important work done by a biochemist less than 40 years old. The Council of the SEBBM acknowledged that the decision to award this prize to **Dr. Sabio** was a difficult one because of the excellent quality of the candidates, but they highlighted **Dr. Sabio's** research into new mechanisms of cell signaling by kinases in stress and metabolic diseases, which have been published in the most important scientific journals such as the *EMBO Journal*, *Nature Communications*, and *PNAS*. **Dr. Sabio** is also first author of several registered patents and has received a large number of scholarships and awards.



XII HEALTH SCIENCES AWARD CAJA RURAL GRANADA FOUNDATION

Dr. Valentín Fuster Carulla, general director of the CNIC and director of the Cardiovascular Institute of the Mount Sinai Medical Center in New York, received the XII Health Sciences Award from the **Caja Rural Granada Foundation** for research on 'Progression of Early Subclinical Atherosclerosis', which is endowed with 20,000 euros and a certificate. The PESA (Progression of Early Subclinical Atherosclerosis) study, the work for which **Dr. Fuster** was awarded, uses state-of-the-art diagnostic vascular imaging technology to try to resolve some of the open questions in cardiovascular pathology, such as when and how it starts and what has to happen for it to become clinically manifest. The project, which began in 2010, includes 4,184 individuals and its main objective is to study the presence and progression of early atherosclerosis using noninvasive imaging technology.

XI MADRI+D AWARDS OF THE MADRI+D FOUNDATION

The XI **madri+d** Awards of the **madri+d Foundation** recognize excellence in the development of international collaborative research and development activities. This year, the **madri+d** Award for Best European R&D Cooperative Project was awarded to the SECURE Project, led by **Dr. Valentín Fuster**, general director of the CNIC and director of the Cardiovascular Institute at the Mount Sinai Medical Center in New York. SECURE (Secondary prEvention of CardiovascUlAr disease in the Elderly population) is a Horizon2020-funded project to conduct a clinical trial to study the efficacy of the polypill in reducing fatal cardiovascular events in patients who recently suffered a myocardial infarction. The trial will enroll 3,600 patients over 65 years of age in Spain, Italy, Germany, France, the Czech Republic, Hungary and Poland. In the project, which has a funding of nearly 6 million euros, 11 institutions from 8 different countries participate. **Dr. José María Castellano**, who coordinates the project together with **Dr. Fuster**, collected the award during the ceremony held on June 29.



BBVA FOUNDATION

Three CNIC projects were selected by the 2016 fellowship and grants program of the **BBVA Foundation**. The team of Dr. Borja Ibáñez Cabeza, Director of Clinical Research at the CNIC, is one of the groups that were awarded a grant through the program 'Grants for Scientific Research Teams. Call 2016', for their project 'Fat diet for heart failure reversal: a conceptual change (Faithful)'. This call is aimed at the realization of projects with high social interest in the fields of basic, translational and applied research in different areas. The project of Dr. Ibáñez, which fell in the area of Cardiology, will receive a grant

of 119,790 € and has a duration of 3 years. The other two grants received by the CNIC, this time in the section of "Grants for Cultural Researchers and Creators 2016", were awarded to **Dr. Rebeca Acín Pérez** and **Dr. María Pilar Martín Fernández**. **Dr. Acín's** project entitled "Characterization of the critical role of mitochondria in the prevention of heart failure", and **Dr. Martín's** project entitled "MicroRNAs as a differential diagnostic tool between Acute Myocarditis and Acute Myocardial Infarction", will have a duration of 6 to 18 months, and each will receive 40,000 €.



LA CAIXA-SEVERO OCHOA PHD FELLOWSHIPS

Six researchers have joined the CNIC with fellowships obtained through the third call of the **la Caixa-Severo Ochoa International PhD Program** and the la Caixa Program for PhD studies at Spanish Universities. The entity continues its scholarship programs with two new calls for fellowships to stimulate excellence in research and social progress. The "la Caixa" Foundation offers 71 fellowships for PhD studies at leading universities and research centers in Spain. This time, the six CNIC researchers are: **Macarena Fernández Chacón**, **Rebeca Torregrosa Carrión**, **Jesús Victorino Santos**, **Álvaro Sahún Español**, **María del Carmen Aboy Pardal** and **José Antonio Valverde López**.

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WHAT'S ON
INSIDE SCIENCE
CNIC & SOCIETY

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